UNIVERSITY OF ALBERTA

Synthesis of 2',3'-Didehydro-2',3'-Dideoxynucleosides and Synthetic Studies on the Farnesyl Transferase Inhibitors CP-225,917 and CP-263,114

by

Paulo W. M. Sgarbi ©

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled **Synthesis of 2',3'-Didehydro-2',3'-Dideoxynucleosides and Synthetic Studies on the Farnesyl Transferase Inhibitors CP-225,917 and CP-263,114** submitted by **Paulo W. M. Sgarbi** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

D. L. J. Clive

Dr. D. L. J. Clive

Dr. N. Dovichi

Dr. J. Stryker

Dr. J. Vederas

John R. Mercer

Dr. J. Mercer

Dr. L. Weiler

(External Examiner)

To my parents, my brothers and
Shirley Ann

ABSTRACT

2',3'-Dimesylates of 5'-*O*-protected nucleosides are converted into the corresponding 2',3'-didehydro-2',3'-dideoxy compounds by treatment with either telluride dianion in the form of the lithium salt, or lithium phenyl selenolate. These methods are well-suited to the preparation of unsaturated nucleosides that can be converted into compounds which are believed to be useful in the treatment of HIV infections (*e.g.* ddI).

The scope of the reactions was investigated, and the deoxygenation with lithium telluride was found to be general for vicinal dimesylates that have, or may adopt, a *syn* periplanar conformation. With acyclic compounds the reaction is stereospecific. The deoxygenation involving lithium phenyl selenolate was found to be general for vicinal dimesylates of ribonucleosides and to work well for dimesylates of internal straight chain vicinal diols. However, this reagent performed poorly in the case of terminal 1,2-dimesylates. The mechanism of the reaction with lithium telluride was investigated, and our experiments support a double nucleophilic displacement pathway over a single electron transfer process. Finally, we attempted to prepare a polymer-supported deoxygenation reagent, based on the chemistry of lithium phenyl selenolate.

The carbobicyclic core of the Ras farnesyl transferase inhibitors CP-225,917 and CP-263,114, was built by an anionic oxy-Cope rearrangement. This method represents a promising approach to the total synthesis of these natural products, and preliminary work towards a more advanced model was carried out. Other approaches, based on radical cyclization, were also investigated, and are reported in this work.

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LIST OF ABBREVIATIONS

Ac	acetyl
AIBN	2,2'-azobis(isobutyronitrile)
Ar	Aryl
B	Purine or pyrimidine base
Bn	benzyl
br s	broad singlet (NMR spectroscopy)
t-Bu	*tert*-butyl
ca.	about
CAN	ceric ammonium nitrate $[(NH_4)_2Ce(NO_3)_6]$
cf.	compare
COSY	correlation spectroscopy
d	day(s); doublet (NMR spectroscopy)
δ	chemical shift (in ppm) from tetramethylsilane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DIBAL-H	diisobutylaluminum hydride
DMSO	dimethyl sulfoxide
DMSO-d_6	deuterated dimethyl sulfoxide
DMT	4,4'-dimethoxytrityl
DNA	deoxyribonucleic acid
DVB	divinylbenzene
Et	ethyl
EWG	electron-withdrawing group
FDA	Food and Drug Administration
FTase	Ras farnesyl transferase
FTIR	Fourrier transform infrared spectroscopy

GDP	guanosine diphosphate
GTP	guanosine triphosphate
h	hour(s)
HIV	human immunodeficiency virus
HMPA	hexamethylphosphoric triamide
Hz	Hertz
IR	infrared spectroscopy
J	coupling constant (NMR spectroscopy)
LDA	lithium diisopropylamide
LG	leaving group
liq	liquid
m	multiplet (NMR spectroscopy)
Me	methyl
min	minute(s)
mg	milligram(s)
MHz	megahertz
mL	milliliter(s)
mmol	millimole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
m/z	mass/charge
NMR	nuclear magnetic resonance spectroscopy
µL	microliter(s)
NOE	nuclear Overhauser effect
Nu	nucleophile
PCC	pyridinium chlorochromate

Ph..............	phenyl
ppm.............	parts per million
q...............	quartet (NMR spectroscopy)
rt..............	room temperature
s...............	singlet (NMR spectroscopy)
SET.............	single electron transfer
Super-Hydride....	lithium triethylborohydride
t...............	triplet (NMR spectroscopy)
TBAF............	tetrabutylammonium fluoride
TBDMS...........	*tert*-butyldimethylsilyl
TCDI............	thiocarbonyldiimidazole
Tf..............	trifluoromethanesulfonyl
THF.............	tetrahydrofuran
TLC.............	thin layer chromatography
Tr..............	triphenylmethyl
T-ROESY.........	rotating frame Overhauser effect spectroscopy
UV..............	ultraviolet

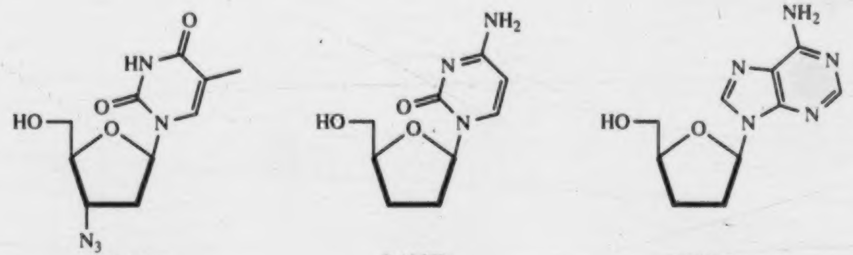
PART I

SYNTHESIS OF 2',3'-DIDEHYDRO-2',3'-DIDEOXYNUCLEOSIDES

I. Introduction

The Importance of Deoxygenated Nucleosides.

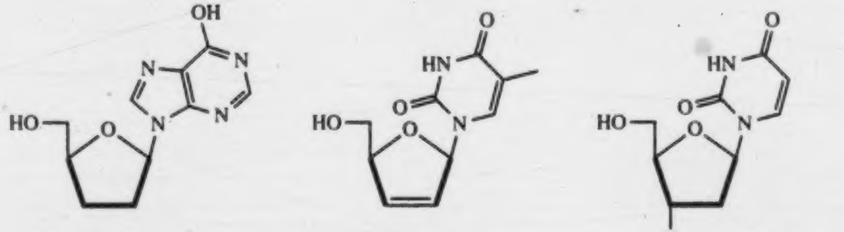
2',3'-Dideoxygenated nucleosides are considered useful drugs in the treatment of HIV infection,[1] and several compounds of this type have received FDA approval in the last few years.[2] These compounds (Figure 1) are AZT (**1**), ddC (**2**), ddI (**4**), and d4T (**5**). AZT (**1**) has long been used clinically. DdI is prepared from ddA by enzymatic



1 (AZT)
3'- azido-3'- deoxythymidine
FDA approved

2 (ddC)
2',3'- dideoxycytidine
FDA approved

3 (ddA)
2',3'- dideoxyadenosine



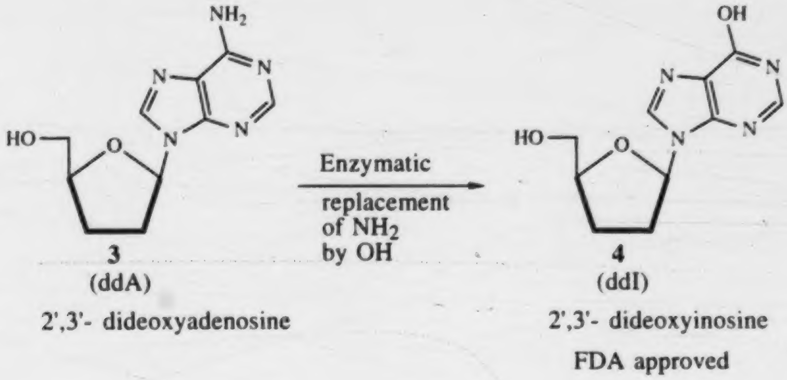
4 (ddI)
2',3'- dideoxyinosine
FDA approved

5 (d4T)
2',3'- didehydro-3'- deoxythymidine
FDA approved

6 (AZddU)
3'- azido-3'- deoxyuridine

Figure 1 *Nucleoside derivatives, some of which are currently used in the treatment of HIV infections.*

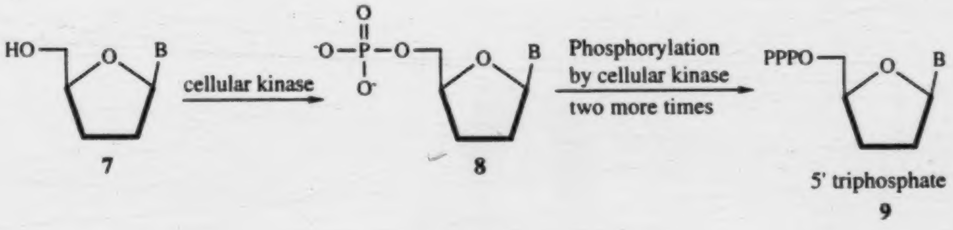
replacement of the NH_2 group by OH (Scheme 1).[3]


NH2
N
N
N
N
HO
O
Enzymatic
replacement
of NH2
by OH
3
(ddA)
2',3'- dideoxyadenosine
OH
N
N
N
N
HO
O
4
(ddI)
2',3'- dideoxyinosine
FDA approved

Scheme 1

Another compound, AzddU (*cf*. Figure 1, compound **6**) has already reached the stage of preliminary clinical trials.[4]

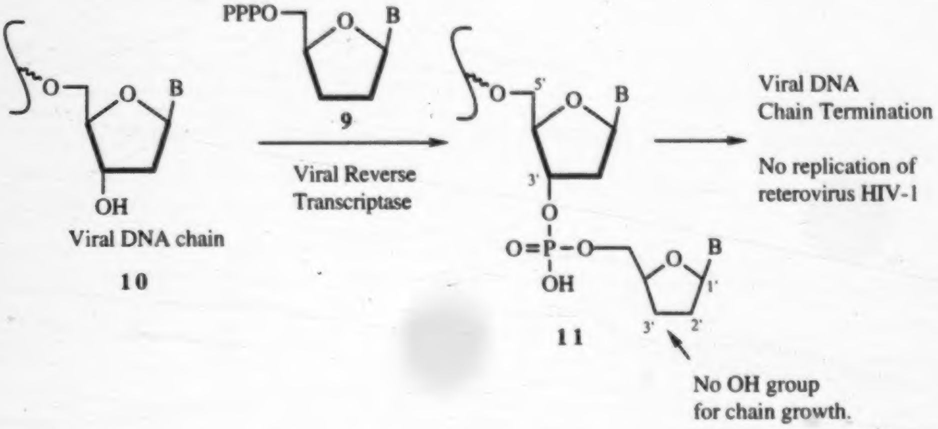
The mechanism of action of these drugs has not yet been fully established. It is accepted that dideoxynucleosides **7** act as pro-drugs and are sequentially phosphorylated by cellular enzymes (kinases) to the 5'-triphosphate **9** (Scheme 2). The efficiency of this phosphorylation


HO
O
B
7
cellular kinase
O
⁻O–P–O
O⁻
O
B
8
Phosphorylation
by cellular kinase
two more times
PPPO
O
B
5' triphosphate
9

Scheme 2

process is not the same for each individual substrate, and this can account for some of the differences in activity observed for the nucleoside derivatives listed in Figure 1.

The 2',3'-dideoxynucleosides, after *in vivo* phosphorylation, block the replication process of the retrovirus HIV-1 (Scheme 3). Normally, replication of HIV involves elongation of a growing DNA chain in the 5'→3' direction. Consequently, a nucleoside lacking a C-3' hydroxyl but still accepted by the viral reverse transcriptase (a DNA polymerase), will be attached *via* its phosphorylated C-5' hydroxyl, to the growing DNA chain. This will cause the chain growing process to terminate, because the product of coupling lacks the requisite functionality at C-3' of the new terminus to permit further chain growth.


PPPO
O
B
9
Viral Reverse
Transcriptase
O
B
OH
Viral DNA chain
10
5'
3'
O=P-O
OH
1'
2'
11
Viral DNA
Chain Termination
No replication of
reterovirus HIV-1
No OH group
for chain growth.

Scheme 3

Another proposed mode of action suggests that either dideoxynucleoside triphosphate **9** (Scheme 2), or the terminated oligonucleotide **11** (Scheme 3), behave as competitive inhibitors of HIV reverse transcriptase.[5] The biochemical pathways which take place for each dideoxynucleoside are complicated, and are still under investigation.[6]

There are, of course, side effects associated with these drugs and they are thought to occur from the fact that the triphosphate **9** as well as the mono- and diphosphate, have affinity for other cellular enzymes.[5] The bone marrow toxicity observed in AIDS patients receiving nucleoside treatment is thought to occur because of the inhibition of thymidylate kinase, which is a cellular enzyme. The peripheral neuropathy reported in patients being treated with ddC and ddI may be due to inhibition of mitochondrial DNA polymerases.[6]

A strategy that has been followed in recent years for development of anti-AIDS drugs is to seek dideoxynucleosides or analogs which are substrates of cellular kinases, and which are triphosphorylated, and are capable of binding to the HIV reverse transcriptase but not to the host enzymes. Multidrug treatments have also been proposed, due to reports of AZT resistance.[7] Recent developments in the synthesis of anti-HIV dideoxynucleosides have primarily focused on modification of the carbohydrate portion of the molecules, since the cellular kinases are more tolerant of these changes than alterations in the base moiety.[4]

Preparation of Dideoxynucleosides.

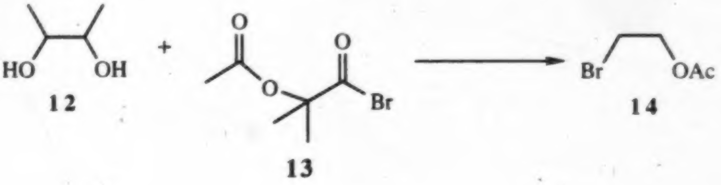
Due to their medical importance, preparation of dideoxynucleosides has been extensively studied. Commercially, the most attractive approach is a ribonucleoside-based route, since the starting materials (ribonucleosides) are readily available, and are relatively inexpensive compared to their 2'-deoxy counterparts. Preparation of dideoxynucleosides and didehydrodideoxynucleosides has been reviewed,[5] and so only a brief summary is given here. Dideoxynucleosides and analogs can also be made by *de novo* synthesis; this subject has also been reviewed[4] and will not be discussed here.

Dideoxynucleosides from Ribonucleosides.

An attractive approach involves converting 5'-*O*-protected nucleoside 2',3'-diols, by means of some type of deoxygenation process, into a double bond. The main methods used in the nucleoside area for converting a 1,2-diol into an olefin are: the Mattocks reaction, the Corey-Winter reaction, the Eastwood olefination, Barton deoxygenation, and the classical Tipson-Cohen method.

1. Mattocks Reaction.

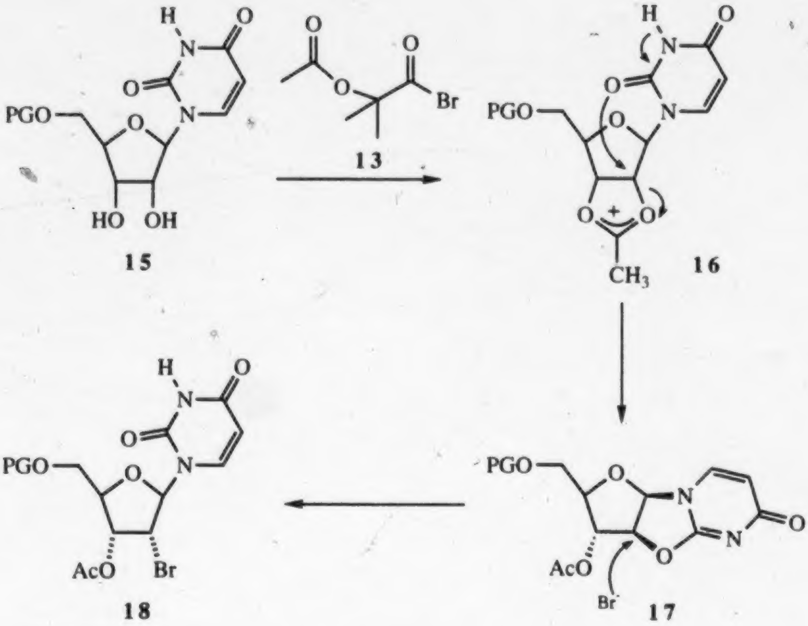
The Mattocks reaction[8] involves treating vicinal diols with α-acetoxyisobutyroyl bromide **13** to form a bromo acetate (Scheme 4).[9,10] Reductive elimination then gives 2',3'-didehydro-2',3'-dideoxynucleosides; various reagents, of which zinc/copper is the most widely used, have been employed in this step.[9] Catalytic hydrogenation of bromo acetate **14** over Pd-C in aqueous acetonitrile in the presence of Na_2CO_3 to yield the dideoxynucleoside, has also been reported.[11]



Scheme 4

This procedure has been used to synthesize at least two of the FDA-approved drugs (ddC[12] and ddI[13]), besides ddA,[14] and ddG.[13] Dideoxynucleosides can be obtained from the 2,3-unsaturated nucleosides by catalytic hydrogenation over Pd-carbon[9] or Raney Ni.[9] D4T has also been synthesized by a process analogous to the Mattocks reaction;[15] in this procedure, acetyl bromide replaces the more expensive α-acetoxyisobutyroyl bromide.

When uridine analogs are subjected to the Mattocks process, the reaction is not only regiospecific but also stereoselective, due to neighboring group participation (Scheme 5).

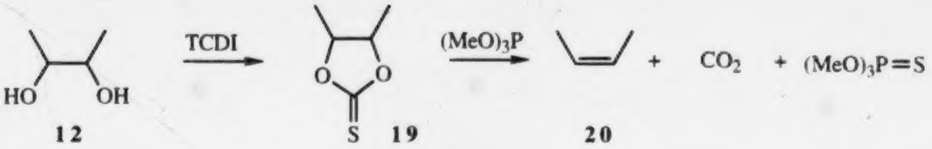


Scheme 5

With compounds unable to form intermediates corresponding to **17**, such as *N*-acetyl cytidine or purine nucleosides, bromo acetate formation is not usually regiospecific.

2. Corey-Winter Reaction.

In the Corey-Winter process[16], a vicinal diol is treated with thiocarbonyldiimidazole, yielding a cyclic thiocarbonate (Scheme 6). By treatment with trimethylphosphite, this intermediate undergoes desulfurization and decarboxylation, giving the desired olefin. The reaction is based on the



Scheme 6

hypothesis that a carbene intermediate (Figure 2), might be formed, and should collapse, giving carbon dioxide and the olefin. Both trimethyl phosphite and triethyl phosphite are

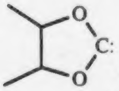
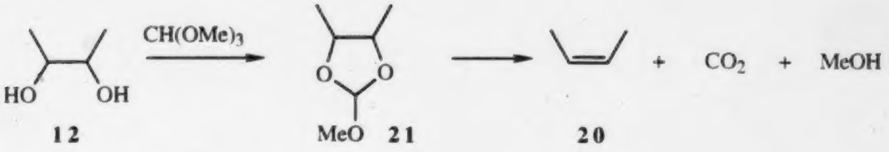


Figure 2 *Proposed carbene intermediate in the Corey-Winter process.*

effective in removing sulfur from the thiocarbonate. In a synthesis of ddU using this method, some *N*-methylation of the pyrimidine base was observed,[17] although this could be avoided by using 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine[18,19] or triethyl phosphite instead of trimethyl phosphite. Other compounds made by the Corey-Winter procedure include ddA, ddG, and ddT with either triethyl phosphite or 1,3-dimethyl-2-phenyl-1,3,2-diazaphospholidine.[19] Yields in some cases are low,[19] and thiocarbonyldiimidazole is fairly expensive.

3. Eastwood Olefination.

In the Eastwood olefination,[20] a vicinal diol is treated with methyl (or ethyl) orthoformate, producing a cyclic orthoformate (Scheme 7), which collapses thermally to the olefin, under acidic conditions.

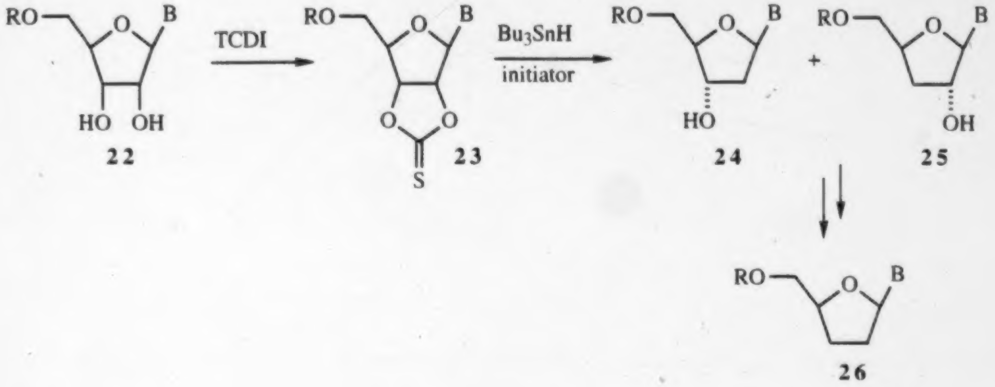


Scheme 7

For acid sensitive compounds, a modification of the original procedure is necessary,[21] and this involves using acetic anhydride as the solvent for the thermal decomposition of the 1,3-dioxolane intermediate. Thus, ddU was prepared from the corresponding cyclic orthoformate by this procedure, although attempts to make ddC and ddA failed due to cleavage of the *N*-glycosyl bond.[22] D4T was obtained by an analogous method,[23] although in low yield.

4. Barton Deoxygenation.

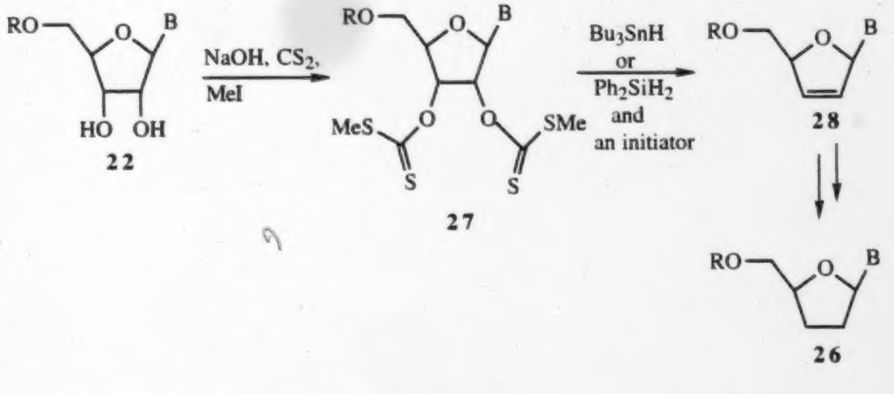
Ribonucleosides can be deoxygenated by Barton's method[24] through two related procedures: in the first (Scheme 8), a vicinal diol is treated with thiocarbonyldiimidazole, producing a cyclic thionocarbonate which, upon reaction with tributyltin hydride, yields a mixture of deoxygenated products.


RO
B
HO OH
22
TCDI
23
S
Bu$_3$SnH
initiator
HO
24
+
OH
25
26

Scheme 8

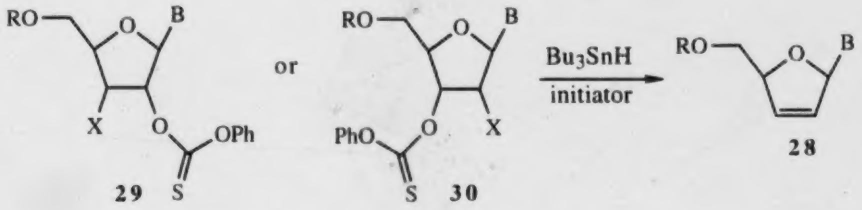
Subjecting this mixture a second time to the same conditions,[25] affords the dideoxygenated product.

In the second method, a bisxanthate is formed by treatment of the vicinal diol with sodium hydroxide, carbon disulfide, and methyl iodide (Scheme 9). Reaction of the bisxanthate with tributyltin hydride then affords the 2',3'-didehydro-2',3'-dideoxynucleoside in high yield.[19]


RO
B
HO OH
22
NaOH, CS$_2$,
MeI
MeS
SMe
S
27
Bu$_3$SnH
or
Ph$_2$SiH$_2$
and
an initiator
28
26

Scheme 9

A few other compounds are known to yield 2',3'-didehydro-2',3'-dideoxynucleosides under radical conditions, *e.g.*, 2',3'-dichloronucleosides[26], 2'-bromo,3'-[(phenoxythiocarbonyl)oxy]nucleosides or 2'-[(phenoxythiocarbonyl)oxy]-3'-bromonucleosides (Scheme 10).[27]



X = Bromine or Chlorine

Scheme 10

The Barton deoxygenation is widely used, and contamination of the final product by tin reagents can be avoided by substituting diphenylsilane for tributyltin hydride. Both ddA and ddU have been synthesized by this modification.[28]

5. Other Methods.

Several other methods have been used for the preparation of 2',3'-dideoxynucleosides from ribonucleosides. *Inter alia*, a photosensitized electron-transfer reaction was used in the deoxygenation of uridine derivatives,[29] and also for the synthesis of purine 3'-azido-2',3'-dideoxynucleosides.[30] Ribonucleoside dimesylates have also been reduced with sodium iodide and zinc dust, yielding the corresponding olefin,[31] although in low yield.

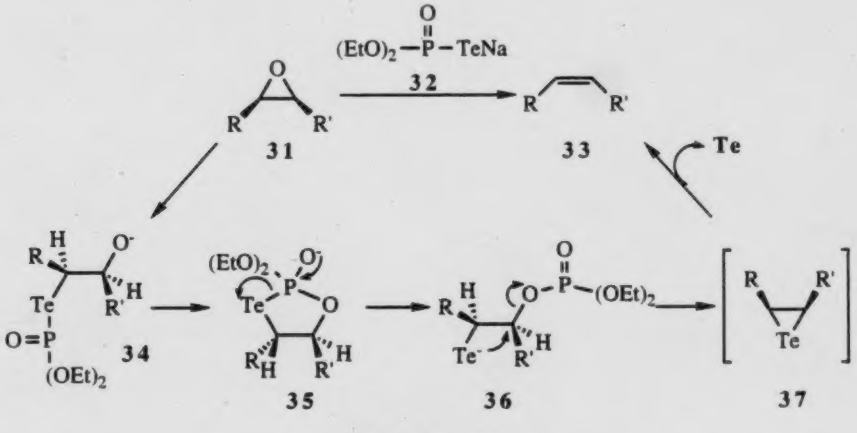
Several methods for the conversion of non-nucleoside diols into olefins have been reported in an exhaustive review by Block,[32] and will not be discussed here.

Although several routes have been examined extensively, as discussed above, the development of new methodology is warranted in view of the importance of the area.

II. Results and Discussion

Background Information.

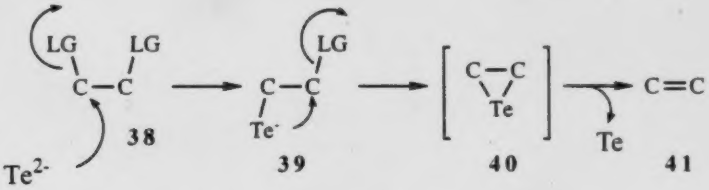
Our approach to the conversion of vicinal diols into olefins was based on a process developed earlier in this laboratory (Scheme 11).[33]



Scheme 11

Sodium diethyl phosphorotelluroate acts as a nucleophile towards epoxides, causing the ring opening. Presumably, intermediate **34** rapidly undergoes a series of intramolecular processes that culminate in the formation of the three-membered ring species **37**. This compound spontaneously expels the heavy atom.[33,34,35]

Based on the mechanism depicted in Scheme 11, one might wonder if vicinal leaving groups could also be converted, transiently, into epitellurides or episelenides, and then into olefins, by the action of nucleophilic tellurium or selenium reagents (Scheme 12).



Scheme 12

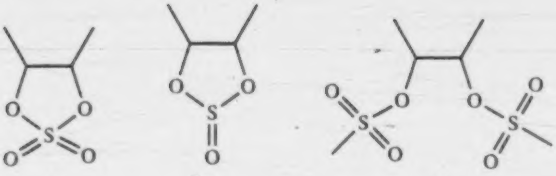
Vicinal dibromides have been converted into olefins by reaction with telluride[36] or selenide[37] dianions. However, for the deoxygenation of ribonucleosides, the leaving group should be one easily derivable from a hydroxyl, and it should be of such a type that the resulting compounds are stable enough for easy handling, and available in good yield. The following sections will briefly describe the methodology that was developed in this laboratory by P. L. Wickens[38] based on the considerations above, and, studied further in my work to establish the scope and mechanism.[39]

Preparation of Te^{2-}.

A number of methods are available[40] for generating Te^{2-} and these were extensively surveyed by P. L. Wickens;[41] Na_2Te, obtained by reaction of sodium and tellurium in liquid ammonia,[40a,40b] was shown to be a very suitable reagent,[39] as is Li_2Te, prepared[39,40m] from tellurium and Super-Hydride (Et_3BHLi in THF); the latter reagent was used extensively throughout the present work. Electrochemical methods have also been used for generating the telluride dianion.[42] These methods were also exhaustively studied by P. L. Wickens,[41] but yields of dideoxydidehydronucleosides were generally poor.[39]

Preparation of Starting Materials.

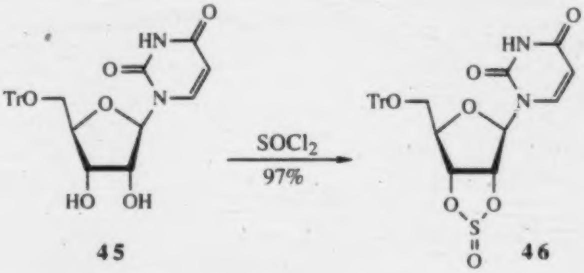
The nature of the leaving group was largely dictated by the fact that our starting materials were ribonucleosides, i.e. vicinal diols. We initially considered using cyclic sulfates, as we expected such species to react with Te^{2-} in the required way.[43] However, for the nucleoside series, preparation of cyclic sulfates (*cf.* **42**, Scheme 13) by oxidation of the corresponding sulfites (**43**) was overall very low-yielding.[44]



42 **43** **44**

Scheme 13

Cyclic sulfites (**43**),[45] in contrast, are easy to prepare but, at least in the case of compound **45** (Scheme 14), do not afford the desired olefins on treatment with Te^{2-}, the starting diol being recovered.[43b,46]



45 **46**

Scheme 14

Dimesylate (*cf.* **44**, Scheme 13) and ditosylate derivatives were then employed,[39] and no difficulties were found in converting vicinal diols into the corresponding dimesylates by the standard method,[47] i.e. treatment of the diol with $MeSO_2Cl/Et_3N$ or $MeSO_2Cl$/pyridine in CH_2Cl_2.

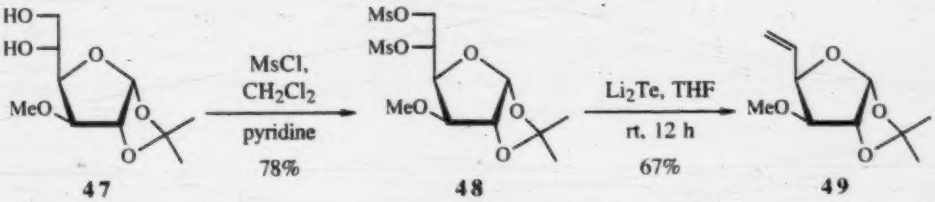
Conversion of Dimesylates into Olefins using Te^{2-}.

The optimum conditions for transformation of vicinal dimesylates into the corresponding olefins by treatment with

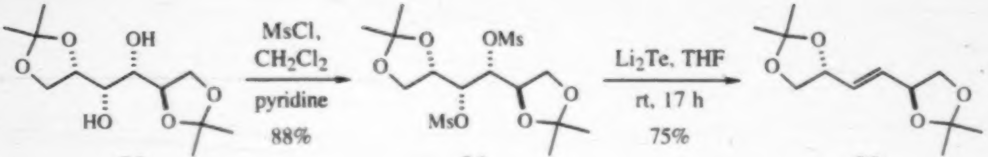
Te^{2-} have been described elsewhere.[38,39,41] Therefore, the effects on this process of changing reaction conditions (i.e. use of different solvents or various temperature) or reagents (i.e. the source of Te^{2-} or the use of Se^{2-} or S^{2-}) will not be discussed. Suffice it to say that, for our purposes, the reagent of choice is lithium telluride (Li_2Te) conveniently prepared *in situ* by addition of Super-Hydride (*vide supra*) to Te,[39] followed by gentle warming (40 °C) for 1 h. The reactions were all carried out in THF at, or above, room temperature.

Nature of the Dimesylate.

In my work it was found that both terminal (*cf.* **48**, Scheme 15) and internal (*cf.* **51**, Scheme 16) acyclic dimesylates undergo the present reaction. In the first case, vicinal dimesylate **48** (prepared from diol **47**[48] in 78% yield) gives terminal olefin **49** in good yield. In the second case, *syn* dimesylate **51** (prepared in 88% yield[49a]



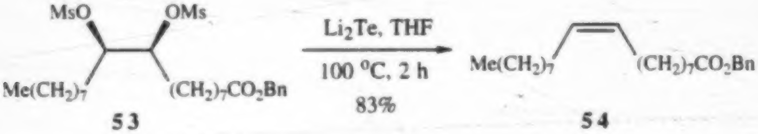
Scheme 15


MsCl,
CH_2Cl_2
pyridine
88%
Li_2Te, THF
rt, 17 h
75%
OH
HO
OMs
MsO

50 **51** **52**

Scheme 16

from diol **50**[49b)] smoothly gives *E*-olefin **52** in 75% yield. This result clearly complements the earlier[38] report from this laboratory on the deoxygenation of *anti* dimesylate **53** (prepared in 95% yield from the parent diol), which affords the corresponding *Z*-olefin **54** in good yield (Scheme 17).

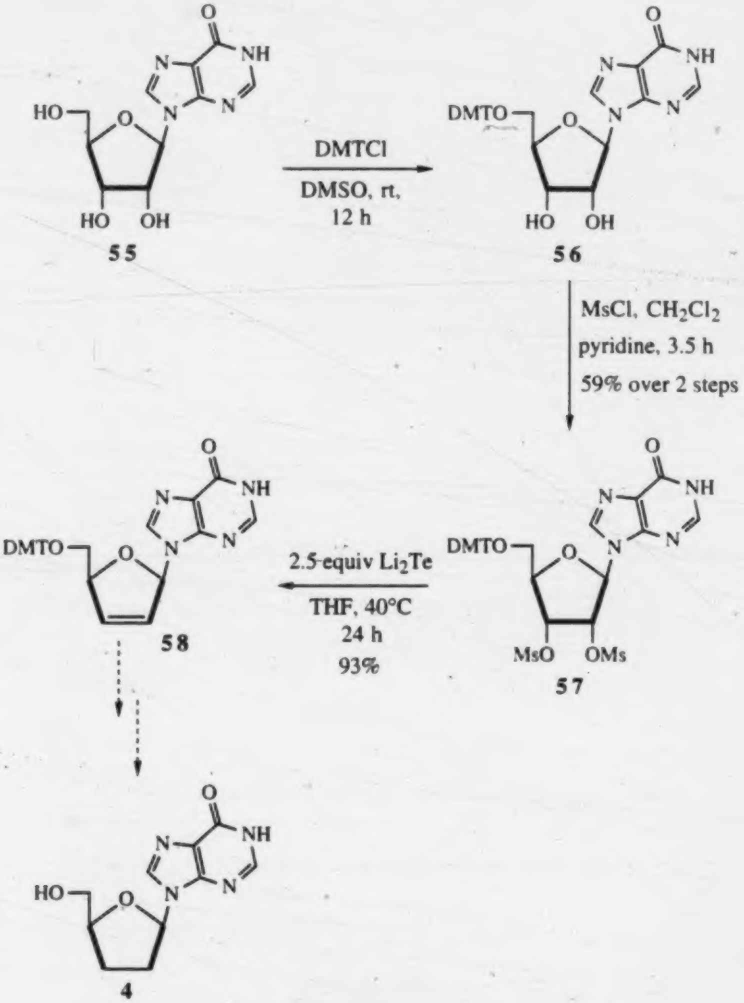

MsO
OMs
Me(CH$_2$)$_7$
(CH$_2$)$_7$CO$_2$Bn
Li_2Te, THF
100 °C, 2 h
83%
Me(CH$_2$)$_7$
(CH$_2$)$_7$CO$_2$Bn

53 **54**

Scheme 17

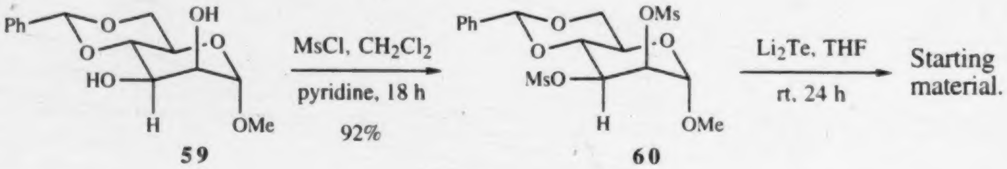
Schemes 16 and 17 illustrate the stereospecific nature of this deoxygenation process.

Regarding dimesylates derived from cyclic diols, the process works remarkably well for the nucleoside series and is quite general, being equally applicable to compounds bearing either purine or pyrimidine bases,[38] and is illustrated by the potential synthesis of ddI (**4**) (Scheme 18). Compound **58** itself has not been converted into ddI, but the corresponding *t*-BuMe$_2$Si derivative has been taken on to ddI,[19] and we assume[39] our reaction would also work in the silylated series.


55
56
57
58
4
DMTCl
DMSO, rt,
12 h
MsCl, CH$_2$Cl$_2$
pyridine, 3.5 h
59% over 2 steps
2.5 equiv Li$_2$Te
THF, 40°C
24 h
93%

Scheme 18

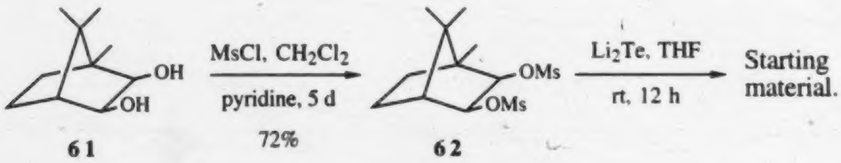
On the other hand, manopyranoside **60** (obtained from diol **59**[50] in 92% yield) is not a suitable substrate (Scheme 19), and only starting material was recovered from the reaction mixture (70%). This fact suggests that the hydroxyl groups must be able to adopt a *syn* coplanar geometry


Ph
O
O
OH
O
HO
H
OMe
59
MsCl, CH_2Cl_2
pyridine, 18 h
92%
OMs
MsO
60
Li_2Te, THF
rt, 24 h
Starting material.

Scheme 19

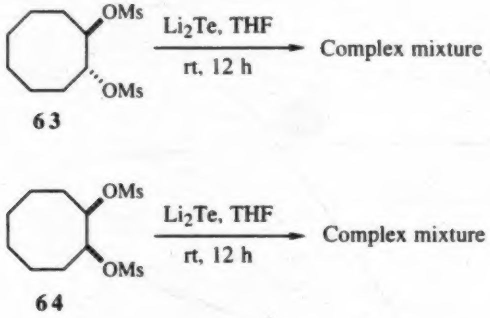
(or close to that). This preferred arrangement is, of course, readily accessible to the acyclic compounds and intrinsic to the ribonucleosides.

Steric factors also have a major influence on the course of this reaction, and the dimesylate derived from the [2.2.1] bicyclic diol **61**[51] (Scheme 20) is not converted into olefin – the material is simply recovered (92%). Notice that, in this case, the hydroxyl groups (and hence the dimesylates) are *syn* coplanar; but *endo* attack by Te^{2-} is disfavored due to steric hindrance to the approach of Te^{2-}.


OH
OH
61
MsCl, CH_2Cl_2
pyridine, 5 d
72%
OMs
OMs
62
Li_2Te, THF
rt, 12 h
Starting material.

Scheme 20

The case of the dimesylates of *cis*- and *trans*-cyclooctane-1,2-diols[52] was also examined (Scheme 21). We wondered if the large and flexible eight-membered ring would be able to adopt the required *syn* coplanar conformation in either instance. However, both cyclooctane substrates gave complex mixtures of products and, as I was unable to isolate and identify any specific compounds, it is not possible to suggest a reason for our observation.

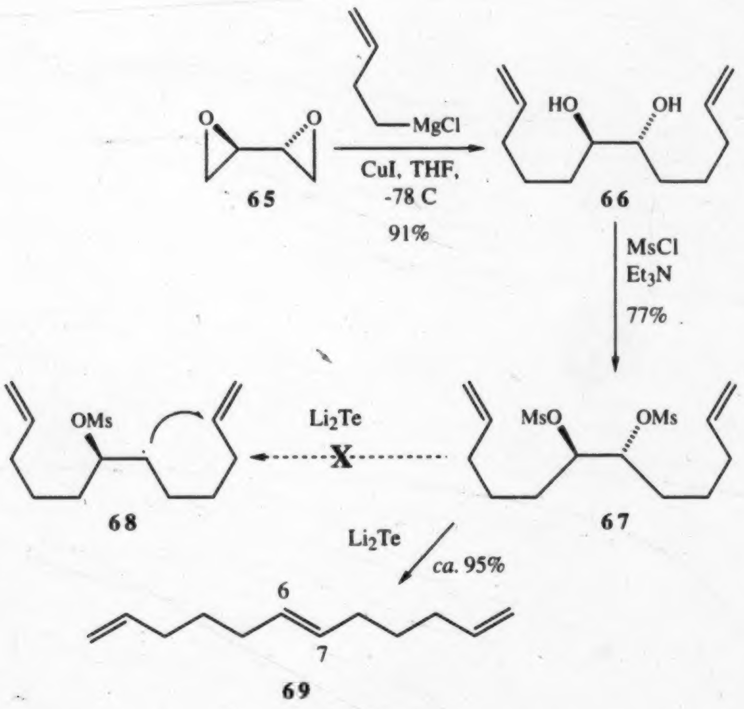


Scheme 21

Mechanistic Considerations.

Several observations support the double nucleophilic displacement pathway for this deoxygenation process (Scheme 12). For instance, the stereochemical outcome observed with the open chain dimesylates **51** (Scheme 16) and **53** (Scheme 17), i.e. the formation of *E* and *Z* olefins, and the sensitivity to steric factors (Scheme 20), are both consistent with this mechanism. However, a single electron transfer (SET) process would also be compatible with our observations. In order to examine this possibility, a simple experiment was designed to trap possible carbon radical intermediates, arising from a SET mechanism.

Diol **66**, prepared from (*S,S*)-1,2,3,4-diepoxybutane **65**[53] by cuprate addition[54] to the more easily accessible primary termini of the molecule, was converted into dimesylate **67** in 77% yield (Scheme 22).


MgCl
CuI, THF,
-78 C
91%
65
66
HO
OH
MsCl
Et$_3$N
77%
OMs
MsO
OMs
Li$_2$Te
X
68
67
Li$_2$Te
ca. 95%
6
7
69

Scheme 22

Dimesylate **67** was then subjected to our standard conditions, but no traces of cyclized product could be detected; olefin **69** was the only isolated product of the reaction (*ca.* 95% yield). The *E*-stereochemistry of the C(6)-C(7) double bond was determined from the value (16 Hz) of the coupling constant of the vinyl hydrogens. A value of *ca.* 8-10 Hz would be observed if the stereochemistry were *Z*. The measurement was made by first irradiating the C(5)/C(8) methylene groups (CD_2Cl_2, δ 1.95-2.10) in order to simplify the spectrum (Figure 3). The coupling constant of the hydrogens on C(6)-C(7) (CD_2Cl_2, δ 5.42) was then measured from the proton satellites corresponding to $R^{13}CH{=}^{12}CHR$. In this situation (i.e. one carbon is ^{13}C and the other is ^{12}C) the molecule is unsymmetrical and the coupling constant can be easily obtained.

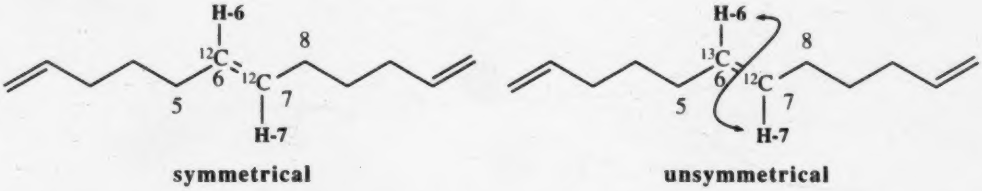


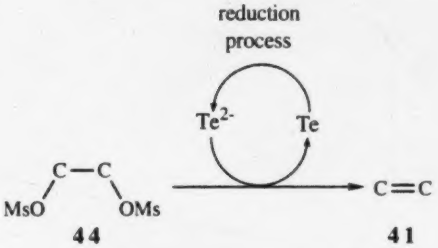
Figure 3 *E relationship between H-6 and H-7 in olefin* ***69***.

In summary, conversion of vicinal diols into the corresponding dimesylates, followed by treatment with Li_2Te (from Te and Et_3BHLi) results in smooth deoxygenation to the olefin in the case of acyclic compounds or nucleosides, and represents a valuable approach for the synthesis of several dideoxynucleosides. Our experiments also show that the most probable pathway for this transformation is a simple double nucleophilic displacement of the vicinal leaving groups, as proposed in Scheme 12.

Development of a Polymer-supported Reagent.

1. Preliminary Investigations.

One interesting characteristic of our deoxygenation methodology is the extrusion of elemental Te. An obvious way to profit from this fact involves the development of a process which is *catalytic* in Te (Scheme 23).



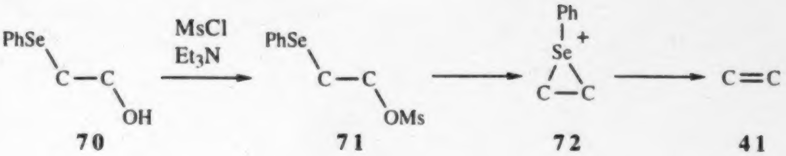
44 **41**

Scheme 23

Studies on this approach have been carried out in this laboratory by P. L. Wickens[41] and, therefore, will not be discussed.

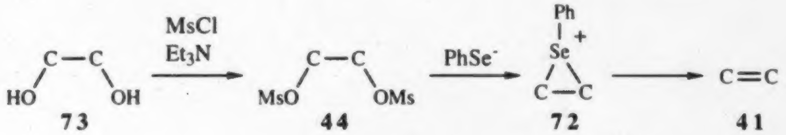
One variation of this theme would require the development of a polymeric reagent. If the nucleophilic tellurium (or selenium) reagent could be attached to an insoluble polymer, recovering and recycling the reagent would become a simple task; the benefits of such process are obvious.

We based our efforts towards a polymer-supported reagent in the following observation: compounds of partial structure **70** afford olefins when the hydroxyl function is converted into a good leaving group, e.g., OMs (Scheme 24).[55]



Scheme 24

We presumed that the same intermediates should also be accessible by displacement, by ArSe⁻ (e.g., PhSe⁻ prepared by reduction of diphenyl diselenide), of a single mesyloxy group from a vicinal dimesylate (Scheme 25).



Scheme 25

If such displacement could be accomplished, then, in principle, a conveniently substituted polystyrene (Figure 4) would be able to perform the same transformation.

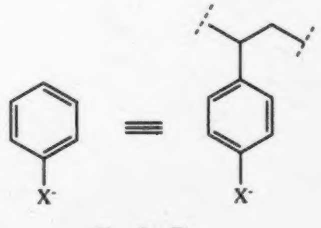
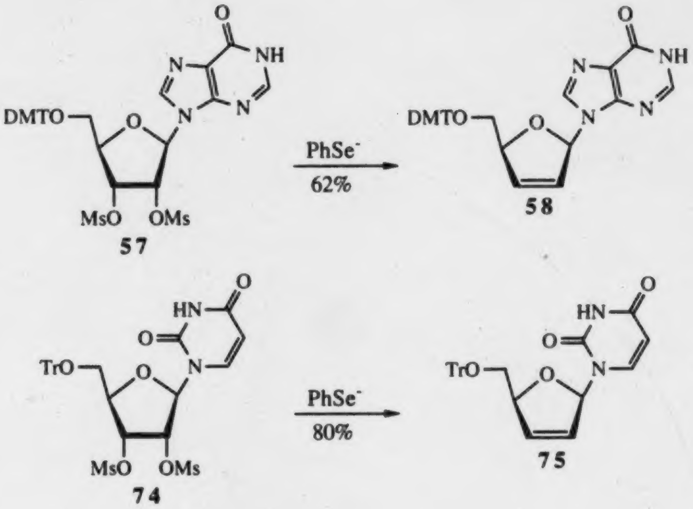


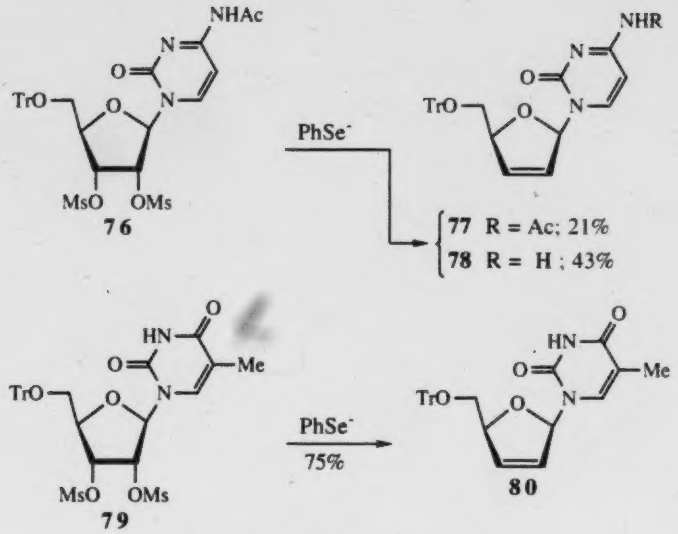
Figure 4 *A polymer-supported reagent based on ArX⁻.*

We have tested the process summarized by Scheme 25, and applied it to a number of compounds, and have found that it represents a very convenient route to olefins of the nucleoside series, as we have reported.[56] A few preliminary experiments along such lines were performed by P. L. Wickens, but are not discussed here.[41]

Four nucleoside dimesylates were examined (Scheme 26) and were converted into the corresponding olefin on treatment with $PhSe^{-}Li^{+}$ (2.5 mol per mol of dimesylate) in refluxing THF, the selenide anion being conveniently generated from diphenyl diselenide and Et_3BHLi.[57] Diphenyl diselenide was regenerated in the process, although we did not systematically measure the amount recovered.



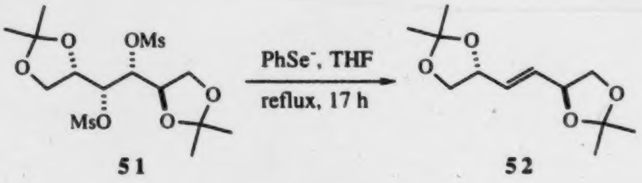
Scheme 26 (*continues*)


NHAc
TrO
MsO OMs
76
PhSe⁻
NHR
TrO
77 R = Ac; 21%
78 R = H ; 43%
HN
Me
TrO
MsO OMs
79
PhSe⁻
75%
80

Scheme 26 (*cont'd.*)

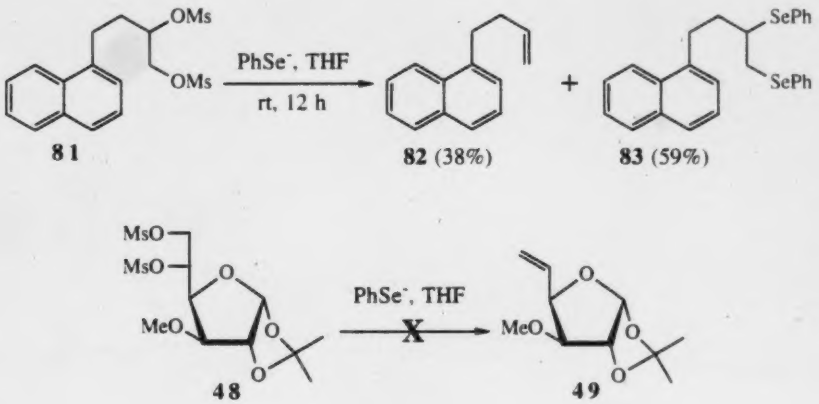
In the case of *N*-acetyl cytidine derivative **76**, the acetyl group was partially removed, but we did not determine whether changing conditions would affect the outcome of the reaction.

We also examined acyclic dimesylates, both internal (*cf.* **51**, Scheme 27) and terminal (*cf.* **81**[41] and **48**, Scheme 28). In the former case, the sugar derivative **51** gave, under our new deoxygenation conditions, *E* olefin **52** in good (77%) yield.


OMs
MsO
51
PhSe⁻, THF
reflux, 17 h
52

Scheme 27

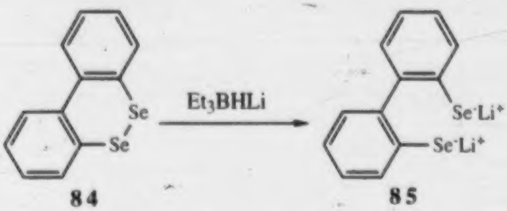
Dimesylates **81** and **48**, however, behaved in a different way. Compound **81** gave a very low yield (38%) of olefin under our standard conditions with PhSe$^-$Li$^+$, along with the bis(phenylselenide) **83**, resulting from displacement of both OMs groups by PhSe$^-$ (Scheme 28). Dimesylate **48** failed to give olefin.



Scheme 28

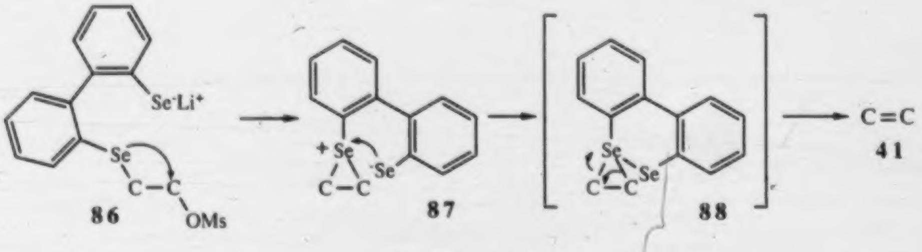
Since it is known that vicinal bis(phenylselenides) can collapse to olefins,[58] we decided to investigate what influence the nature of the aryl selenolate might have on this process.

We first examined the cyclic compound **84**[59] (Scheme 29). We wondered if dianion **85** (generated by treatment of **84** with Et$_3$BHLi) would be able to displace the vicinal


Et$_3$BHLi
Se
Se
Se⁻Li⁺
Se⁻Li⁺
84
85

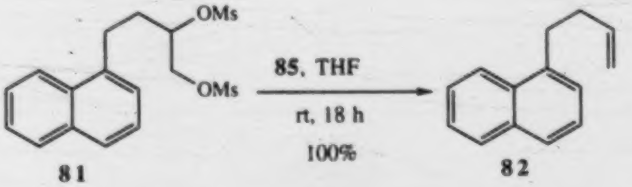
Scheme 29

OMs groups and, by an intramolecular process (Scheme 30), facilitate the formation of olefin.


Se⁻Li⁺
Se
C—C
OMs
86
+Se
Se⁻
C—C
87
Se
Se
C—C
88
C=C
41

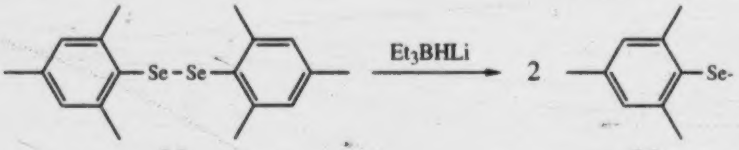
Scheme 30

Although dianion **85** worked remarkably well for terminal dimesylate **81** (Scheme 31), this behavior was not general: the more sterically congested ribonucleosides could not be deoxygenated by dianion **85**. Diselenin **84** was recovered from the reaction mixture involving **81** in excellent yield (91%).


OMs
OMs
85, THF
rt, 18 h
100%
81
82

Scheme 31

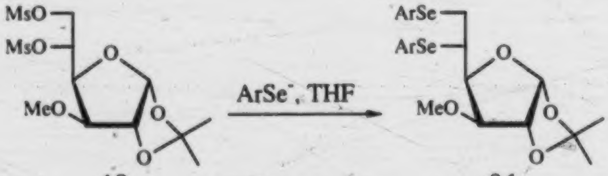
The case of glucose derivative **48** suggests that displacement of only one OMs group could perhaps be achieved if a sterically more demanding reagent was employed: the steric hindrance posed by the arylseleno group would probably inhibit a second displacement, and the reaction would then follow the desired course. For this purpose, we prepared diaryl diselenide **89**,[60] which gives selenolate **90** by treatment with Et_3BHLi (Scheme 32).



89 **90**

Scheme 32

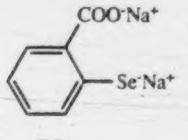
Compound **48** was then treated with selenolate **90**, but the only identifiable product had both OMs groups displaced by the selenolate (Scheme 33).



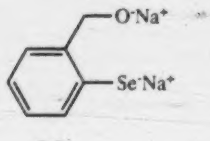
48 **91**

Scheme 33

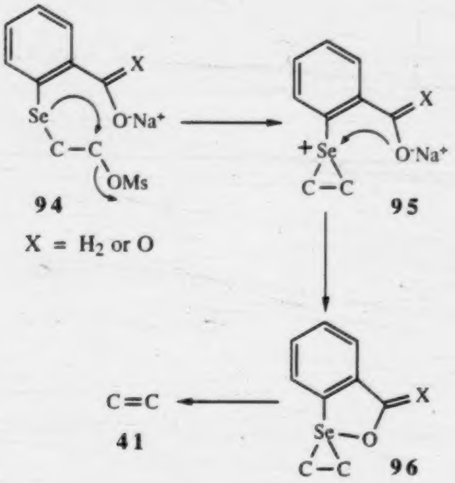
Finally, we examined selenides **92**[61] and **93**,[62] hoping that the intramolecular process depicted in Scheme 34 might occur, and hence facilitate the deoxygenation.



92



93


X
Se
O⁻Na⁺
C−C
OMs
94
X = H₂ or O
+Se
95
C=C
41
Se−O
96

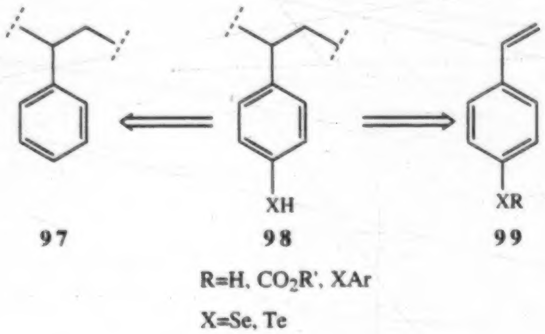
Scheme 34

Using dimesylate **81** as a test case, no olefin could be detected after treatment with either dianions **92** or **93**.

At this point, we decided to halt our investigations on the effect of the nature of the aryl selenolate on the course of the reaction. Since we had observed that PhSe$^-$ was a satisfactory deoxygenating agent for ribonucleosides, we moved on to try the development of a polymeric reagent based on that substructure.

2. Preparation of Se- and Te-Containing Polymers.

Our goal was to prepare a polymer (*cf.* **98**, Scheme 35) containing ArX^- groups (X = Se or Te) able to mimic the nucleophilic behavior of $PhSe^-$ towards vicinal dimesylates. We sought to achieve this by either functionalizing commercially available polystyrenes (*cf.* **97**, Scheme 35), or by preparing a suitably substituted monomer (*cf.* **99**, Scheme 35) that would subsequently be polymerized.



Scheme 35

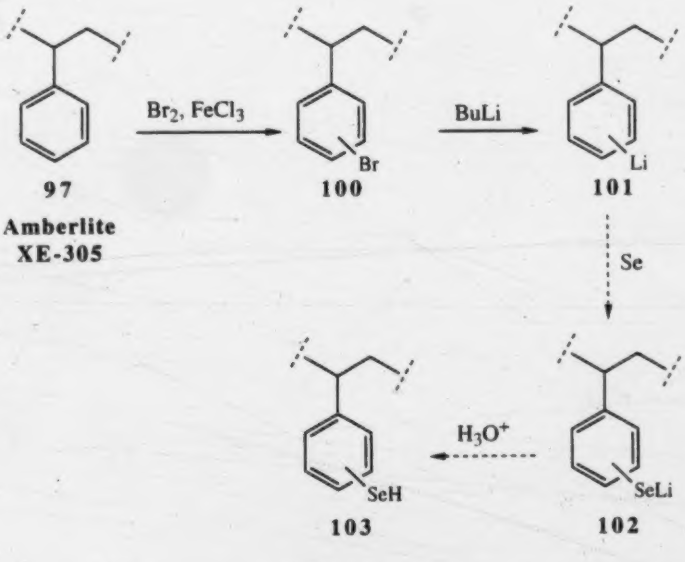
We also thought that, ideally, the ArX^- substructures should be distributed in pairs throughout the backbone of the polymer, since we observed that, in the cases of $PhSe^-$ and dianion **85**, the corresponding diselenides were regenerated in the reaction mixture (*vide supra*).

Our approaches to accommodate these ideas will be discussed in the following sections.

2a. Modification of Commercially Available Polymers.

This approach was pioneered in this laboratory by P. L. Wickens, whose work towards the functionalization of Merrifield's resin and polystyrenes has been described elsewhere,[41] and will not be dealt with here.

Our first attempt at functionalization of polystyrene resins was based on analogous work by Fréchet *et al.*[63] These authors reported the preparation of a polymeric thiol by treatment of lithiated polystyrene with a THF suspension of sulfur. We followed the same procedure, but using selenium instead of sulfur (Scheme 36).

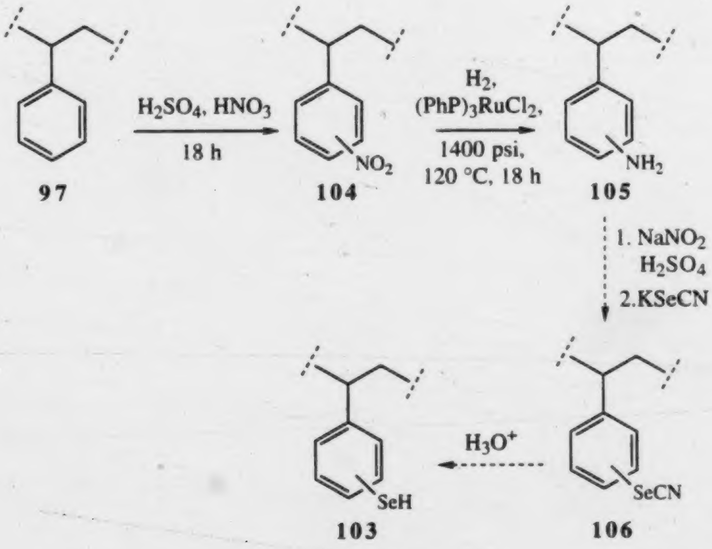


Br_2, $FeCl_3$
BuLi
Br
Li
Se
H_3O^+
SeH
SeLi
97
Amberlite
XE-305
100
101
102
103

Scheme 36

Thus, brominated polystyrene **100** was treated with *n*-BuLi, affording lithiated resin **101**. Selenium was then added to a suspension of this resin in THF. After a prolonged reaction time, the mixture was quenched, and the resin was thoroughly washed and then dried. The resulting material, however, did not seem to contain Se [absence of IR-active SeH *ca.* 2300 cm^{-1}), and elemental analysis].

We also attempted to prepare a selenium-containing polymer by a procedure reported by Kato *et al.*[64] (Scheme 37).


97
H_2SO_4, HNO_3
18 h
NO_2
104
H_2,
$(PhP)_3RuCl_2$,
1400 psi,
120 °C, 18 h
NH_2
105
1. $NaNO_2$
H_2SO_4
2. KSeCN
SeCN
106
H_3O^+
SeH
103

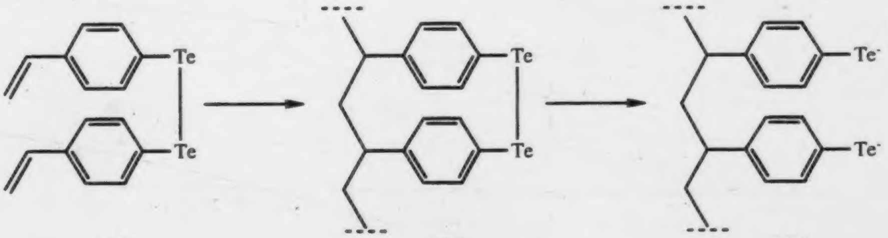
Scheme 37

This method was based on the reaction between a diazonium salt and KSeCN (*via* S_NAr), followed by hydrolysis of the selenocyanate to the corresponding selenol. We prepared poly(aminostyrene) **105** by catalytic hydrogenation of easily accessible poly(nitrostyrene) **104**[65] in a homogeneous solution of dichlorotris(triphenylphosphine)ruthenium (II) in 1:1 benzene-ethanol,[66] and the IR spectrum of the polymer obtained this way was similar to that of an authentic sample.[65] In our hands, however, the key step did not seem to generate the selenocyanate **106**, since the IR absorption expected for the cyano group (*ca.* 2200 cm^{-1}) was absent in the product.

2b. Preparation of Polymeric Reagents by Polymerization of Suitable Monomers.

2b.1 Template approach.

According to Scheme 35, another possible way to prepare the desired polymers is by polymerization of selenium- or tellurium-containing monomers. Our initial attempts were based on a template approach proposed by Brill.[67] In a situation like this (Scheme 38), the aryl tellurolate groups



107 **108** **109**

Scheme 38

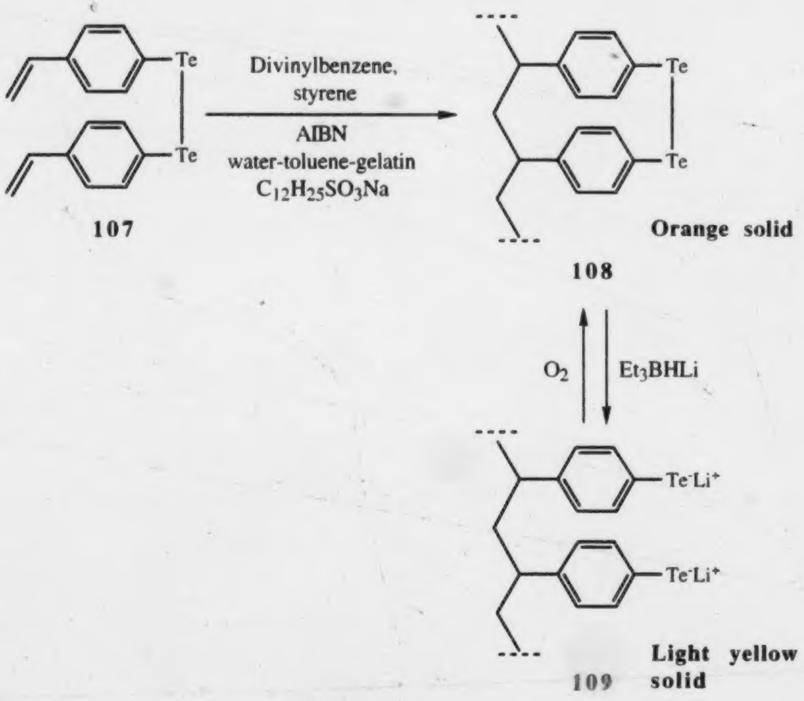
are regularly disposed in the polymer matrix and interaction of these two groups should be sterically favored.

The required bis(*p*-vinylphenyl) ditelluride **107** was prepared according to the literature directions (from the *p*-vinylphenyl Grignard reagent, by reaction with Te in the presence of O_2)[68] and copolymerized with divinylbenzene and styrene. The original communication by Brill[67] does not give details on the polymerization process, and so I will discuss our approaches in more detail.

a. Aqueous Suspension Polymerization.[69]

This technique gives crosslinked particles with large pore volumes. We presumed, rightly or wrongly, that a polymer with this morphology would be favorable to the deoxygenation process, by facilitating contact between the reactive sites of the polymer and the substrate.

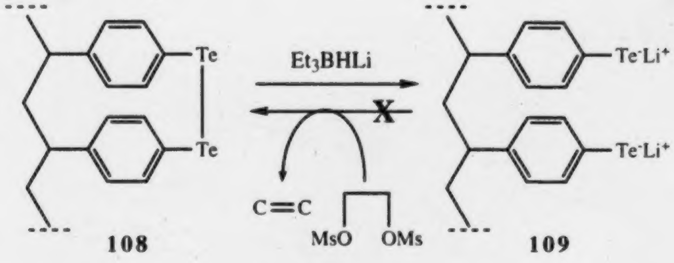
Thus, we prepared polymer **108** by suspension polymerization, guided by a literature procedure (Scheme 39).[70] The orange pellets obtained by this method (the parent compound **107** is an orange-red crystalline solid), after being thoroughly washed to free them of unreacted monomeric species, were treated with Et_3BHLi in THF, afford-


Te
Te
Divinylbenzene,
styrene
AIBN
water-toluene-gelatin
$C_{12}H_{25}SO_3Na$
107
Te
Te
Orange solid
108
O_2
Et_3BHLi
Te^-Li^+
Te^-Li^+
Light yellow solid
109

Scheme 39

ing a suspension of a light yellow solid. Upon exposure to air, the material slowly acquires the original orange color. We interpret this as representing the reversible reduction of the polymer-bound ArTeTeAr to the corresponding polymer-bound ArTe$^-$ (*cf.* Scheme 39, **108→109**), followed by reoxidation of the aryl tellurolate moieties (*cf.* Scheme 39, **109→108**). A THF solution of ditelluride **107**, submitted to the same conditions, shows similar behavior.

We next examined whether polymer **108** could effect the desired deoxygenation. Dimesylates **48**, **51**, **74**, and **81** (that we take as being representative of the scope of our original deoxygenation method) were treated with the new reagent (Scheme 40).



Scheme 40

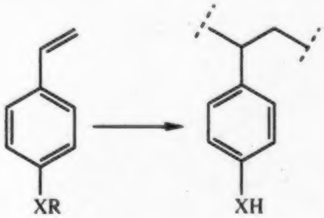
Although variable amounts of olefin were observed in initial tests with dimesylate **81**, we suspect that this result is due to the presence of soluble oligomeric compounds that cause the small amount of deoxygenation that we observed. When resin that had been treated with Et_3BHLi and washed with THF was used, no traces of olefin could be detected after addition of dimesylates. The polymer would, however, reacquire the original orange color when exposed to air.

b. Simple Copolymerization.

Copolymerization of ditelluride **107** with divinylbenzene (AIBN used as initiator) in the absence of solvent also afforded an insoluble resin which displayed the same behavior towards Et_3BHLi as **108**. However, the desired deoxygenation could not be achieved with this resin either.

2b.2 Random Polymerization Approach.

The copolymerization of compounds of general structure **99** with divinylbenzene should generate polymers with randomly placed ArXR groups (Scheme 41).



99 **98**

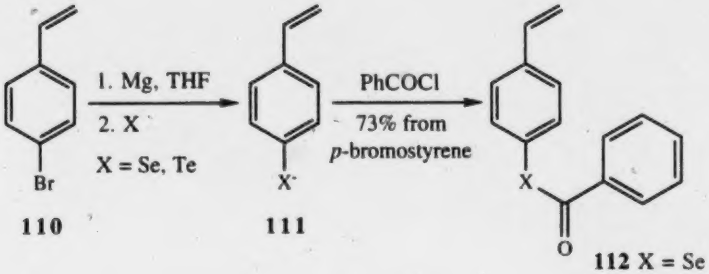
R = H, C(O)R', XAr

X = Se, Te

Scheme 41

The polymerization of aryl selenols (*cf.* **99**, X = Se, R = H, Scheme 41) has been described by Michels *et al.*,[71] and represents the starting point of our efforts. Following the literature procedure, several batches of Se-containing resins were prepared. The original report implies that the polymers are insoluble in organic solvents, but in our hands, the polymers tended to be rather soluble in THF, especially after treatment with Et_3BHLi. Using **81** as a test case, formation of the corresponding olefin was observed, but the reaction did not go to completion; no olefin was detected in the case of uridine derivative **74**.

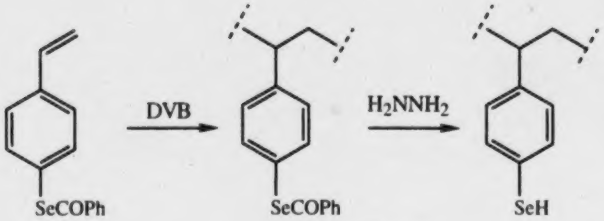
Seeking alternative ways to prepare polymers that were consistently *insoluble* in THF and to gain some control over the distribution of Se in the polymer matrix, we prepared selenoester **112** (Scheme 42, X = Se), by *in situ* acylation of arylselenolate **111** (X = Se) with benzoyl chloride. Compound **112** can be easily isolated and is remarkably stable; furthermore, treatment of **112** with hydrazine smoothly yields the corresponding selenol. Telluroester **113** can be prepared by the same sequence of reactions, but this compound is unstable, unlike the Se-analog.



110 **111** **112** X = Se **113** X = Te

Scheme 42

Copolymerization of **112** with divinylbenzene gave resin **114** which, upon treatment with hydrazine, yields polymer **103**. This material is insoluble in THF (Scheme 43).



112 **114** **103**

Scheme 43

The structural assignment of polymer **103** was based on the disappearance of the carbonyl signal (1675 cm^{-1}) in the IR spectrum. The polymer was treated with Et_3BHLi, washed with THF, and the resulting material was used as a potential deoxygenation reagent, with **81** as a test case. No olefin could be detected.

Conclusions

Conversion of vicinal diols into the corresponding dimesylates, followed by treatment with Li_2Te (from Te and Et_3BHLi) represents a very effective means for deoxygenation when the two mesyloxy groups have or can attain a syn coplanar arrangement. This method is especially useful in the nucleoside series.

A related deoxygenation – which is actually limited to the nucleoside series – can be effected by use of PhSeLi. Attempts to extend this latter process to polymeric reagents were not successful, although we do appreciate that our survey was of a very preliminary nature as we did not rigorously characterize the selenium or tellurium-containing polymers that we prepared. It is planned to carry out a more thorough study of this polymer chemistry in this laboratory.

III. Experimental Section.

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[72] and then through a similar column of Drierite. All solvents for reactions were dried, as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[73] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry tetrahydrofuran (THF), Et_2O, and $PhCH_3$ were distilled from sodium benzophenone ketyl. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. HMPA was distilled from CaH_2 under reduced pressure (oil pump), and kept under Ar atmosphere over molecular sieves. All other solvents were used as purchased. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

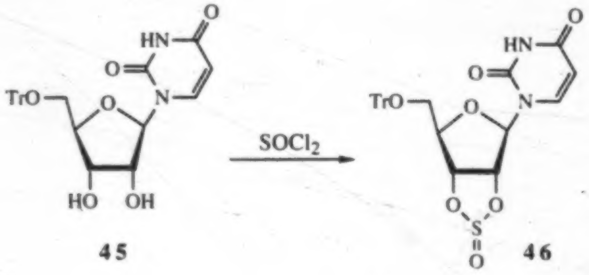
FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

^1H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with AEI Models MS-12 or MS-50 mass spectrometers at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department. Compounds isolated by flash chromatography were homogeneous by TLC and, unless otherwise stated, were pure as judged by high field ^1H NMR spectra.

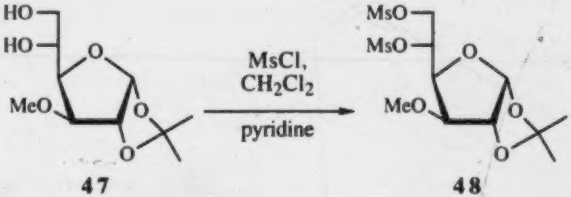
5'-*O*-(Triphenylmethyl)uridine 2',3'-Cyclic Sulfite (46).



45 **46**

$SOCl_2$ (0.06 mL, 0.8 mmol) was added dropwise to a stirred and cooled (0 °C) solution of 5'-*O*-(triphenylmethyl)-uridine (**45**) (222 mg, 0.457 mmol) and pyridine (0.09 mL, 1 mmol) in CH_2Cl_2 (10 mL). After 15 min, the ice bath was removed and stirring was continued for 24 h. The mixture was poured onto ice (*ca*. 15 g) and extracted with CH_2Cl_2 (1 x 5 mL). The organic extract was washed with saturated aqueous $CuSO_4$ (1 x 3 mL), saturated aqueous $NaHCO_3$ (1 x 2 mL), water (2 x 1 mL) and brine (1 x 2 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:1 EtOAc-hexane, gave **46** (201.8 mg, 83%) as a colorless oil that consisted of a 2.5:1 mixture of diastereoisomers: FTIR (CH_2Cl_2 cast) 3202, 3060, 1694, 1219, 1003 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ (major isomer only) 3.47 (dd, J = 11.0, 3.5 Hz, 1 H), 3.54 (dd, J = 11.0, 5.0 Hz, 1 H), 4.34 (dd, J = 9.0, 4.0 Hz, 1 H), 5.56 (dd, J = 8.0, 2.0 Hz, 1 H), 5.65 (dd, J = 6.5, 4.0 Hz, 1 H), 5.69 (dd, J = 6.5, 2.5 Hz, 1 H), 5.87 (d, J = 2.5 Hz, 1 H), 7.25-7.50 (m, 16 H), 9.65 (br s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ (major isomer only) 63.60 (t'), 84.84 (d', two overlapping signals), 87.31 (d'), 87.91 (s'), 92.15 (d'), 103.45 (d'), 127.80 (d'), 128.40 (d'), 128.98 (d'), 141.71 (d'), 143.61 (s'), 150.43 (s'), 163.42 (s'); exact mass *m/z* calcd for $C_{28}H_{24}N_2O_5$ (M - SO_2) 468.1685, found 468.1680.

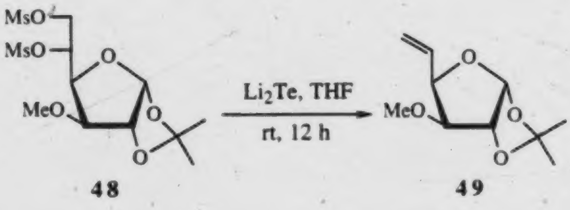
5,6-Di-*O*-methanelsulfonyl-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose (48).



47 **48**

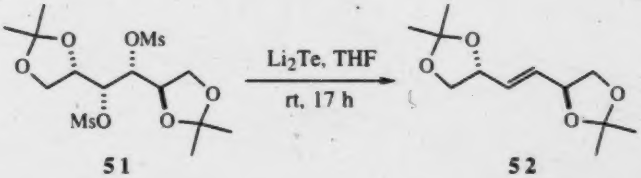
$MeSO_2Cl$ (1.82 mL, 23.7 mmol) was added dropwise over 50 min to a stirred and cooled (ice bath) solution of 1,2-*O*-isopropylidene-3-*O*-methyl-α-D-glucofuranose[48] (**47**) (1.11 g, 4.74 mmol) and pyridine (3.10 mL, 37.9 mmol) in CH_2Cl_2. The mixture was stirred at 0 °C for 10 min, and the cold bath was then removed. Stirring was continued for 18 h, and the mixture was poured onto ice (*ca*. 50 g), and extracted with EtOAc (3 x 35 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 20 mL), aqueous $CuSO_4$ (10%$^w/_v$, 2 x 50 mL), and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 7:3 EtOAc-hexane, gave dimesylate **48** (1.45 g, 78%) as a crystalline solid: mp 78-79 °C; FTIR (CH_2Cl_2 cast) 3000, 1350, 1180 cm^{-1}; ^{1}H NMR (CDCl$_3$, 200 MHz) δ 1.31 (s, 3 H), 1.49 (s, 3 H), 3.06 (s, 3 H), 3.12 (s, 3 H), 3.45 (s, 3 H), 3.85 (d, J = 1.8, 1 H), 4.36 (dd, J = 9.0, 3.0 Hz, 1 H), 4.44 (dd, J = 9.0, 5.4 Hz, 1 H), 4.60 (d, J = 3.0 Hz, 1 H), 4.66 (dd, J = 9.0, 1.9 Hz, 1 H), 5.16-5.21 (m, 1 H), 5.89 (d, J = 3.0 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) δ 26.26 (q'), 26.90 (q'), 37.70 (q'), 39.16 (q'), 57.79 (q'), 68.99 (t'), 74.30 (d'), 77.82 (d'), 80.93 (d'), 82.68 (d'), 105.43 (d'), 112.50 (s'); exact mass *m/z* calcd for $C_{11}H_{19}O_{10}S_2$ (M - CH$_3$) 375.0420, found 375.0419.

General Procedure for Deoxygenation using Li$_2$Te: 5,6-Dideoxy-1,2-*O*-isopropylidene-3-*O*-methyl-α-D-xylo-hex-5-enofuranose (49).



Te powder (200 mesh, 187.6 mg, 1.470 mmol) and a small stirring bar were placed in a dry round-bottomed flask fused onto a reflux condenser. The flask was closed with a septum and flushed with Ar. A solution of Et$_3$BHLi (1 M in THF, 3.8 mL, 3.8 mmol) was injected, and the mixture was stirred at 75 °C (oil bath) until a milky white suspension had formed (*ca.* 30 min). The suspension was cooled down to room temperature, and dimesylate **48** (573.4 mg, 1.4703 mmol) in THF (5 mL) was then injected dropwise. Stirring was continued for 12 h. The mixture was washed out of the flask with Et_2O, and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:1 EtOAc-hexane, gave **49** (183 mg, 67%) as a clear oil, identical to an authentic[74] sample.

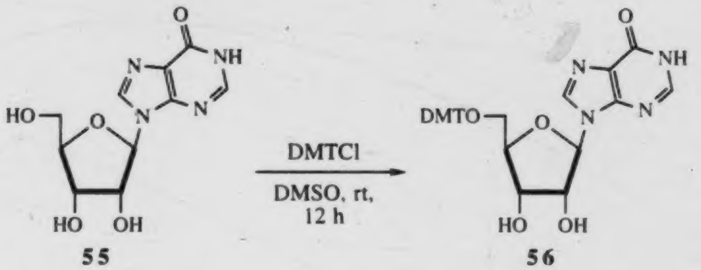
(*E*)-3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-*erythro*-3*E*-hex-3-enitol (52). Use of Li_2Te.



51 **52**

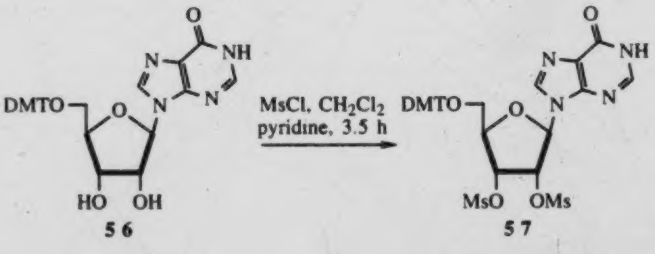
The general procedure was followed, but with minor changes, using Te powder (200 mesh, 191.1 mg, 1.498 mmol), Et_3BHLi (1 M in THF, 3.9 mL, 3.9 mmol), an initial reaction time of *ca*. 30 min at 70 °C (bath temperature), 1,2:5,6-di-*O*-isopropylidene-3,4-di-*O*-methylsulfonyl-D-glucitol[49] (**51**) (626.3 mg, 1.4983 mmol) in THF (5 mL) (injected over 2 h at room temperature), and a reaction time of 15 h. The mixture was washed out of the flask with CH_2Cl_2 and evaporated. Flash chromatography of the residue over silica gel (3 x 16 cm), using 3:7 EtOAc-hexane, gave **52**[75,76] (254.5 mg, 75%) as a crystalline solid (needles): mp 70-71 °C (lit.[75,76] 69-71 °C).

5'-*O*-(4,4'-Dimethoxytrityl)inosine (56).


HO
O
N
N
NH
N
O
HO
OH
55
DMTCl
DMSO, rt,
12 h
DMTO
O
N
N
NH
N
O
HO
OH
56

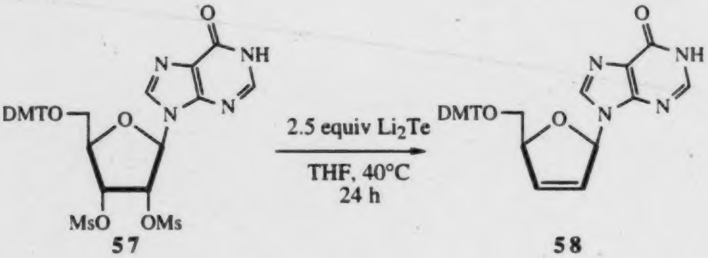
Pyridine (2 mL) was injected into a stirred solution of inosine (**55**) (268.2 mg, 0.9999 mmol) and 4,4'-dimethoxytrityl chloride (441 mg, 1.30 mmol) in dry DMSO (6 mL). Stirring was continued for 12 h. The mixture was poured onto ice, and extracted with $CHCl_3$. The combined organic extracts were washed successively with saturated aqueous $NaHCO_3$ (5 mL), water (2 x 10 mL), and brine (5 mL). The organic solution was dried ($MgSO_4$), diluted with PhMe, and evaporated (water pump). The residue was taken up in PhMe, and again evaporated. Finally, the residue was kept under oil pump vacuum to remove traces of PhMe. The crude 5'-*O*-protected inosine **56** was used directly in the next step.

5'-*O*-(4,4'-Dimethoxytrityl)inosine-2',3'-dimethanesulfonate (57).


DMTO
O
N
N
NH
N
O
HO
OH
56
MsCl, CH2Cl2
pyridine, 3.5 h
DMTO
O
N
N
NH
N
O
MsO
OMs
57

$MeSO_2Cl$ (0.23 mL, 3.0 mmol) in CH_2Cl_2 (3.0 mL) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of 5'-*O*-(4,4'-dimethoxytrityl)inosine (**56**) (432.1 mg, 0.7573 mmol) in pyridine (8 mL). After 10 min, the ice bath was removed and stirring was continued for 3.5 h. The mixture was poured onto ice (*ca*. 10 g) and extracted with CH_2Cl_2 (100 mL). The organic extract was washed with water (10 mL), saturated aqueous $NaHCO_3$ (2 x 5 mL), water (10 mL), and brine, dried ($MgSO_4$), diluted with PhMe, and evaporated (water pump). Evaporation from PhMe was repeated twice more. Finally, the residue was kept under oil pump vacuum to remove traces of PhMe. Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 90:8:2 $CHCl_3$-MeOH-MeCN, gave **57** (402.2 mg, 59% over two steps) as a colorless oil: FTIR (CH_2Cl_2 cast) 3057, 2934, 1699, 1510, 1367, 1251 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.07 (s, 3 H), 3.09 (s, 3 H), 3.41 (dd, J = 11.5, 3.8 Hz, 1 H), 3.61 (dd, J = 11.5, 3.0 Hz, 1 H), 3.75 (s, 3 H), 3.76 (s, 3 H), 4.48 (dd, J = 8.3, 3.5 Hz, 1 H); 5.61 (dd, J = 5.5, 5.0 Hz, 1 H), 6.04 (t, J = 5.5 Hz, 1 H), 6.23 (d, J = 5.5 Hz, 1 H); 6.75-7.50 (m, 13 H), 7.95 (s, 1 H), 8.02 (s, 1 H), 12.25 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 38.72 (q'), 55.61 (q'), 62.40 (t'), 76.15 (d'), 77.17 (d'), 82.44 (d'), 86.74 (d'), 87.34 (s'), 113.61 (d'), 126.18 (s'), 127.46 (d'), 128.33 (d'), 128.43 (d'), 130.46 (d'), 135.45 (s'), 135.60 (s'), 144.75 (s'), 158.63 (s'), 159.24 (s') (the signals corresponding to carbons 2, 4 and 8 in the purine base were not detected under the experimental conditions employed, and several signals of the aromatic groups overlap); exact mass *m/z* calcd for $C_{21}H_{19}O_2$ (M - $C_{12}H_{15}O_9N_4S_2$) 303.1385, found 303.1383.

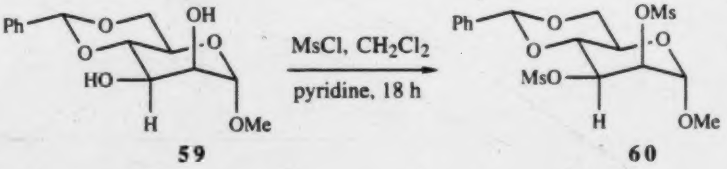
5'-*O*-(4,4'-Dimethoxytrityl)-2',3'-didehydro-2',3'-dideoxyinosine (58).



The general procedure was followed, using Te powder (oven dried at 120 °C for 24 h, 200 mesh, 45.1 mg, 0.353 mmol), Et_3BHLi (1 M in THF, 0.74 mL, 0.74 mmol), an initial reaction time of 1 h at 40 °C, 5'-*O*-(4,4'-dimethoxytrityl)-inosine-2',3'-dimethanesulfonate (**57**) (100 mg, 0.138 mmol) in THF (5 mL). The mixture was stirred at 40 °C for 24 h. At this stage all of the dimesylate had reacted (TLC, silica, 7.5:1.8:0.7 CH_2Cl_2-BuOAc-MeOH). The mixture was cooled, washed out of the flask with CH_2Cl_2, and evaporated at room temperature. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 3:47 MeOH-CH_2Cl_2, gave **58** (68.8 mg, *ca.* 93%) as an off-white solid containing slight impurities (^{1}H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 3058, 2909, 1703, 1509, 1250 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 3.22 (dd, *J* = 4.0, 4.0

Hz, 1 H), 3.38 (dd, J = 6.3, 6.3 Hz, 1 H), 3.8 (s, 6 H), 5.1 (br s, 1 H), 6.09 (d, J = 5.8 Hz, 1 H), 6.42 (d, J = 6.0 Hz, 1 H), 6.70-6.80 (m, 4 H), 7.05 (br s, $W_{1/2}$ = 6.4 Hz, 1 H), 7.15-7.42 (m, 9 H), 7.85 (s, 1 H), 8.28 (s, 1 H), 12.84 (s, 1 H); ^{13}C NMR (CD_2Cl_2, 100 MHz) δ 55.55 (q'), 65.92 (t'), 86.68 (s'), 87.05 (d'), 89.06 (d'), 113.04 (d'), 125.05 (s'), 125.32 (d'), 127.18 (d'), 128.14 (d'), 128.41 (d'), 130.33 (d'), 130.38 (d'), 135.14 (d'), 135.91 (s'), 136.00 (s'), 138.75 (d'), 145.08 (d'), 145.77 (d'), 149.33 (s'), 159.04 (s'), 159.29 (s') (several signals of the aromatic groups overlap); mass (FAB) *m/z* calcd for $C_{31}H_{28}N_4O_5$ (M) 536.2, found 536.3.

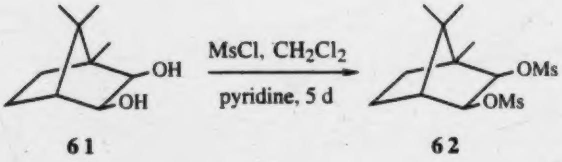
Methyl 4,6-*O*-Benzylidene-α-D-mannopyranoside-2,3-dimethanesulfonate (60).



$MeSO_2Cl$ (0.20 mL, 2.6 mmol) was added over 20 min to a stirred and cooled (0 °C) solution of methyl 4,6-*O*-benzylidene-α-D-mannopyranoside[50] (**59**) (140 mg, 0.497 mmol) and pyridine (0.35 mL, 4.3 mmol) in CH_2Cl_2 (3 mL). After a further 15 min, the ice bath was removed, and stirring was continued for 18 h. The mixture was poured onto crushed ice (*ca.* 5 g) and washed successively with 10%$^w/_v$ aqueous $CuSO_4$

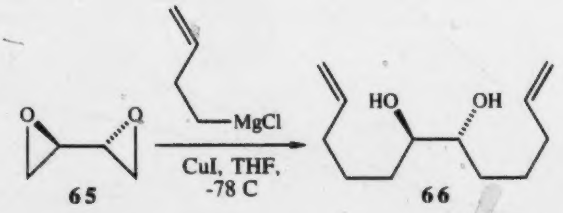
(until a constant blue color was maintained in the aqueous layer), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine. The organic extract was dried ($MgSO_4$) and evaporated. The resulting oil was triturated with Et_2O, and the dimesylate **60** (201.1 mg, 92%) was obtained as a crystalline solid: mp 200-202 °C; FTIR (CH_2Cl_2 cast) 3036, 2940, 1173, 1076, 968, 955 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 3.0 (s, 3 H), 3.27 (s, 3 H), 3.44 (s, 3 H), 3.82-3.96 (m, 2 H), 4.05-4.15 (m, 1 H), 4.28-4.36 (m, 1 H), 4.90-4.95 (m including s at δ 4.94, 2 H in all), 5.05-5.09 (m, 1 H), 5.6 (s, 1 H), 7.35-7.50 (m, 5 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 38.74 (q'), 38.82 (q'), 55.02 (q'), 64.20 (d'), 68.86 (t'), 75.67 (d'), 76.11 (d'), 78.38 (d'), 100.44 (d'), 102.46 (d'), 126.40 (d'), 128.71 (d'), 129.65 (d'), 137.30 (s'); exact mass *m/z* calcd. for $C_{16}H_{22}O_{10}S_2$ 438.0654, found 438.0644.

(±)-2-*exo*-3-*exo*-Camphanediol 2,3-Dimethanesulfonate (62).



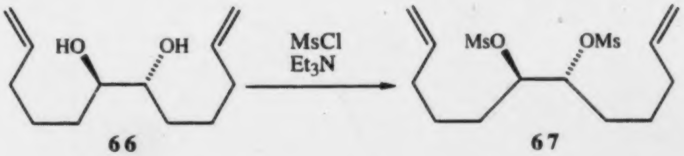
MeSO$_2$Cl (0.39 mL, 5.0 mmol) was added over 60 min to a stirred and cooled (ice bath) solution of (±)-2-*exo*-3-*exo*-camphane-2,3-diol[51] (**61**) (170 mg, 1.00 mmol) and pyridine (0.65 mL, 8.0 mmol) in CH_2Cl_2 (5 mL). The mixture was stirred at 0 °C for a further 10 min, the cold bath was removed, and stirring was continued for 5 d, at which point a major product was detected by TLC (silica, 10% EtOAc-CH_2Cl_2). The mixture was poured onto crushed ice (*ca*. 9 g) and washed successively with saturated aqueous $NaHCO_3$ (2 x 10 mL), aqueous $CuSO_4$ (10% w/v, 4 x 10 mL) and brine (10 mL). The organic solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:9 EtOAc-CH_2Cl_2, gave **62** (233.3 mg, 72%): mp 95-97 °C; FTIR ($CHCl_3$ cast) 2962, 1354, 1175, 1033, 963, 880 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.83 (s, 3 H), 1.00 (s, 3 H), 1.10-1.20 (m including s at δ 1.12, 5 H in all), 1.55-1.90 (m, 2 H), 2.12 (d, J = 5.3 Hz, 1 H), 3.09 (s, 6 H), 4.59 (d, J = 7.0 Hz, 1 H), 4.69 (d, J = 7.0 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 11.20 (q'), 20.49 (q'), 20.75 (q'), 23.38 (t'), 32.58 (t'), 38.56 (q'), 38.63 (q'), 47.72 (s'), 49.41 (s'), 50.72 (d'), 81.93 (d'), 85.62 (d'); exact mass *m/z* calcd for $C_{11}H_{18}O_3S$ (M - CH_3SO_3H) 230.0977, found 230.0977.

(6*S*,7*S*)-1,11-Dodecadiene-6,7-diol (66).



4-Bromo-1-butene (678.3 mg, 5.024 mmol) was added dropwise to a stirred suspension of Mg (174.2 mg, 7.167 mmol) in Et_2O (2 mL) at such a rate that the mixture refluxed gently. The mixture was refluxed for 30 min after the end of the addition (oil bath at 40 °C) and then allowed to cool. The resulting Grignard reagent[54] was then added dropwise over 5 min by syringe to a stirred and cooled (-30 °C) suspension of anhydrous CuI (66.7 mg, 0.350 mmol) in THF (5 mL). After a further 5 min, (*S,S*)-1,2,3,4-diepoxybutane[53] (**65**) (115.8 mg, 1.347 mmol) was added over 15 min. The cold bath was removed and replaced by an ice-bath, and stirring was continued for 1.5 h. Saturated aqueous NH_4Cl was then added to the cold suspension, and the mixture was extracted with Et_2O (2 x 10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 2:3 EtOAc-hexane, gave **66** (208.1 mg, 91%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3373, 3076, 2996 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.33-1.65 (m, 8 H), 1.98-2.16 (m, 4 H), 2.25 (br s, $W_{1/2}$ = 7.0 Hz, 2 H), 3.32-3.42 (m, 2 H), 4.91-5.07 (m, 4 H), 5.75-5.89 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 25.34, 33.40, 34.06, 74.65, 114.70, 139.18; exact mass *m/z* calcd for $C_{12}H_{22}O_2$ 198.1620, found 198.1620.

(6*S*,7*S*)-1,11-Dodecadienyl-6,7-diol Dimethanesulfonate (67).

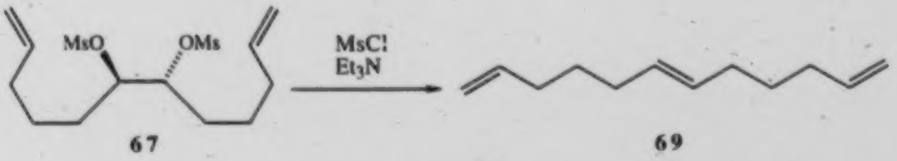


66

67

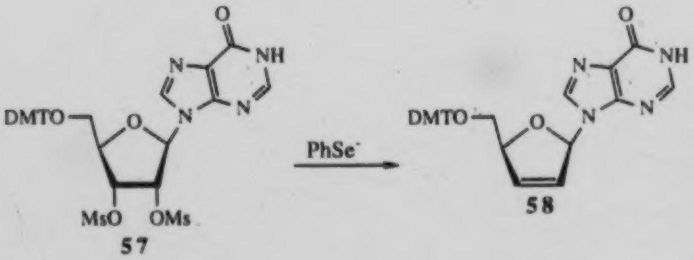
$MeSO_2Cl$ (0.23 mL, 3.0 mmol) was added over 15 min to a stirred and cooled (0 °C) solution of diol **66** (142.1 mg, 0.7177 mmol) and pyridine (0.29 mL, 3.6 mmol) in CH_2Cl_2 (1.4 mL). The ice bath was removed, and stirring was continued for 6 h. The mixture was poured onto crushed ice (*ca.* 5 g) and washed successively with saturated aqueous $CuSO_4$ (2 x 8 mL), water (10 mL), saturated aqueous $NaHCO_3$ (2 x 10 mL), and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 3:7 EtOAc-hexane, gave **67** (195.0 mg, 77%) as a yellow oil: FTIR (CH_2Cl_2 cast) 2940, 1356, 1174 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.48-1.59 (m, 4 H), 1.63-1.87 (m, 4 H), 2.02-2.20 (m, 4 H), 3.06 (s, 6 H), 4.72-4.79 (m, 2 H), 4.95-5.07 (m, 4 H), 5.72-5.88 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 24.30 (t'), 29.99 (t'), 33.49 (t'), 39.07 (q'), 81.20 (d'), 115.49 (t'), 138.21 (d'); mass (CI) *m/z* calcd for $C_{14}H_{26}O_6S_2$ 354.1, found 372.2 (M + 18); exact mass *m/z* calcd for $C_7H_{12}O_3S$ (M - $C_7H_{14}O_3S$) 176.0507, found 176.0507.

(6*E*)-1,6,11-Dodecatriene (69).



The general procedure was followed, but with minor changes, using Te powder (89.6 mg, 0.702 mmol), Et_3BHLi (1 M in THF, 1.46 mL, 1.46 mmol), an initial reaction time of *ca.* 60 min at 40 °C (oil bath), dimesylate **67** (226.2 mg, 0.6381 mmol) in THF (1.3 mL) (added at room temperature), and a reaction time of 2 h. The dark brown suspension was then filtered through a small pad of Celite, and evaporated. Kugelrohr distillation (25 °C, 0.1 mmHg) of the resulting yellow liquid gave **69**[77] (99.6 mg, 95%) as a colorless, volatile liquid, containing slight (<4%) impurities (^{1}H NMR, 300 MHz): FTIR (CH_2Cl_2 cast) 3076, 2977, 1265 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.38-1.50 (m, 4 H), 1.96-2.10 (m, 8 H), 4.92-5.04 (m, 4 H), 5.39-5.44 (m, 2 H), 5.76-5.90 (m, 2 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 29.34 (t'), 32.43 (t'), 33.64 (t'), 114.49 (t'), 130.74 (d'), 139.42 (d'); exact mass *m/z* calcd for $C_{12}H_{20}$ 164.1565, found 164.1568.

General Procedure for Deoxygenation using PhSe$^-$Li$^+$: 5'-*O*-(4,4'-Dimethoxytrityl)-2',3'-didehydro-2',3'-dideoxy-inosine (58).



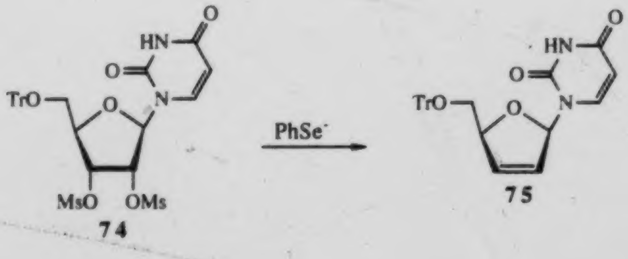
57

58

Et$_3$BHLi (1 M in THF, 0.52 mL, 0.52 mmol) was added dropwise by syringe to a stirred solution of PhSeSePh (79.7

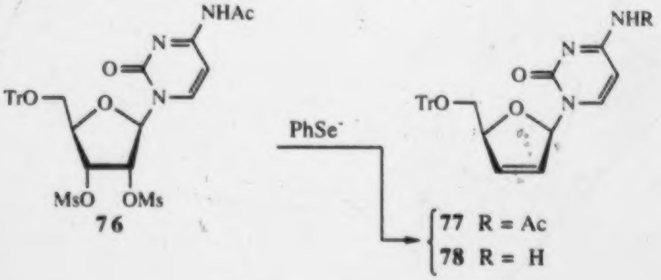
mg, 0.255 mmol) in THF (1 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed, and then **57** (72.6 mg, 0.255 mmol) in THF (1.5 mL) was injected, followed by Et_3N (0.5 mL) and HMPA (40 µL). The solution was refluxed and stirred for 20 h, and then cooled and evaporated at room temperature. Flash chromatography of the residue over silica gel (1 x 25 cm), using 5% $MeOH-CH_2Cl_2$, gave **58** (33.2 mg, 62%), identical to an authentic sample and, like that sample, containing slight impurities (^1H NMR, 300 MHz).

2',3'-Didehydro-2',3'-dideoxy-5'-*O*-(triphenylmethyl)uridine (75).



The general procedure was followed, using Et_3BHLi (1.0 M in THF, 1.1 mL, 1.1 mmol), PhSeSePh (156 mg, 0.498 mmol) in THF (2.5 mL), dimesylate **74** (128 mg, 0.200 mmol) in THF (2.5 mL), Et_3N (1.0 mL) and HMPA (40 µL), and a reflux period of 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm), using 1% $MeOH-CH_2Cl_2$ and then 2% $MeOH-CH_2Cl_2$, gave **75**[15] (72.6 mg, 80% yield) as a white solid, spectroscopically identical to an authentic sample (^1H NMR): mp 190-192 °C (lit.[15] 188-191 °C).

N-Acetyl-2',3'-didehydro-2',3'-dideoxy-5'-O-(triphenylmethylcytidine (77) and 2',3'-Didehydro-2',3'-dideoxy-5'-O-(triphenylmethyl)cytidine (78).

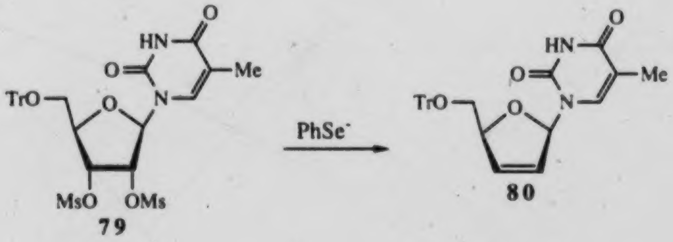


76

77 R = Ac
78 R = H

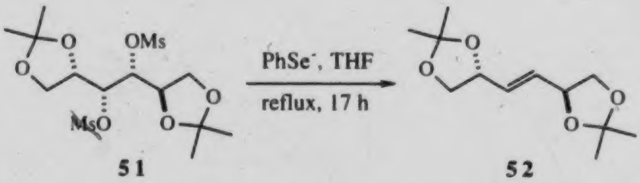
Et_3BHLi (1.0 M in THF, 0.73 mL, 0.73 mmol) was added dropwise by syringe to a stirred solution of PhSeSePh (114 mg, 0.366 mmol) in THF (1 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed. This was taken up into a syringe and added dropwise to a stirred solution of **76** (105 mg, 0.153 mmol) in THF (1.5 mL) (Ar atmosphere). Then Et_3N (0.5 mL) and dry HMPA (*ca.* 40 µL) were injected, and the solution was stirred and refluxed for 22 h. Evaporation of the solvent, and flash chromatography of the residue over silica gel (2 x 18 cm), using 7.5% MeOH-CH_2Cl_2, gave **77**[41] (15.7 mg, 21%) along with 2',3'-dideoxy-2',3'-didehydro-5'-*O*-(triphenylmethyl)cytidine (**78**) (30.0 mg, *ca.* 43%), which was not obtained pure. The material (**78**) had: FTIR (CH_2Cl_2 cast) 3500-3100 (two broad peaks) cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 3.1-3.4 (m, 2 H); 4.9 (br s, 1 H), 5.8 (d, J = 6 Hz, 1 H), 6.2 (d, J = 6 Hz, 1 H), 6.9 (s, 1 H), 7.1-7.4 (m, 16 H), 7.6 (d, J = 7 Hz, 1 H) (the signals corresponding to -NH_2 were not easily discerned); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 65.48 (t'), 86.03 (d'), 87.43 (s'), 91.01 (d'), 94.85 (d'), 127.59 (d'), 127.73 (d'), 128.28 (d'), 129.08 (d'), 133.53 (d'), 142.38 (d'), 143.90 (s'), 156.39 (s'), 166.31 (s'). The mass spectrum (EI) was uninformative, as the highest mass peak corresponded to Ph_3C.

2',3'-Didehydro-2',3'-dideoxy-5-methyl-5'-*O*-(triphenylmethyl)uridine (80).



The general procedure was followed, using Et_3BHLi (1.0 M in THF, 0.49 mL, 0.49 mmol), PhSeSePh (76.9 mg, 0.246 mmol) in THF (1 mL), dimesylate **79**[78] (64.7 mg, 0.0985 mmol) in THF (1.5 mL), Et_3N (0.5 mL) and HMPA (*ca.* 20 μL), and a reflux period of 12 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 2% MeOH-CH_2Cl_2, gave **80**[79] (34.5 mg, 75%) as a white solid: mp 105-109 °C (lit.[79] 107-111 °C).

(*E*)-3,4-Dideoxy-1,2:5,6-di-*O*-isopropylidene-*erythro*-3*E*-hex-3-enitol (52). Use of $PhSe^-Li^+$.

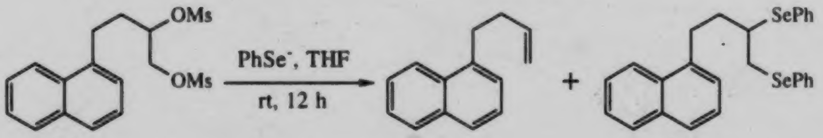


51

52

The general procedure was followed, using Et_3BHLi (1 M in THF, 0.94 mL, 0.94 mmol), PhSeSePh (144 mg, 0.460 mmol) in THF (1.5 mL), dimesylate **51**[49] (76.9 mg, 0.184 mmol) in THF (1.5 mL), Et_3N (0.92 mL) and HMPA (40 µL), and a reflux period of 17 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2.5 x 20 cm), using 25% EtOAc-hexane, gave **52**[75,76] (32.3 mg, 77%) as a white solid, identical to an authentic sample (*vide supra*): mp 69-70 °C (lit.[75,76] 69-71 °C).

1-(3-Butenyl)naphthalene (82). Use of $PhSe^-Li^+$.



81

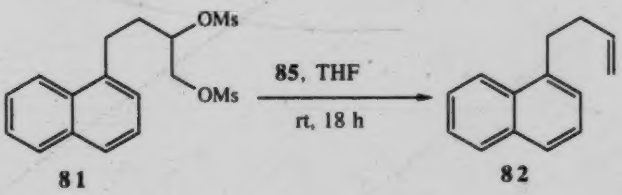
82

83

The general procedure was followed, using Et_3BHLi (1.0 M in THF, 0.2 mL, 0.2 mmol), PhSeSePh (31.2 mg, 0.100 mmol) in THF (1 mL), dimesylate **81** (37.3 mg, 0.100 mmol) in THF (1.5 mL), Et_3N (0.5 mL) and HMPA (40 µL), and a reaction time of

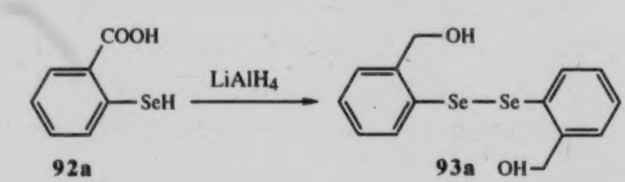
12 h at room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 15 cm), using petroleum ether, gave **82** (7.0 mg, 38%). The byproduct of this reaction was isolated (59%) and identified as the bis(phenylselenide) **83** corresponding to displacement of both OMs groups: FTIR (CH_2Cl_2 cast) 3067, 3054, 2925, 1476, 1436, 735, 690 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.99 (m, 1 H), 2.51 (m, 1 H), 3.5-3.0 (m, 5 H), 7.09-7.60 (m, 14 H), 7.73 (d, J = 7.2 Hz, 1 H), 7.88 (m, 1 H), 8.09 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75 MHz) δ 31.33, 34.94, 35.18, 45.01, 124.27, 125.88, 126.20, 126.62, 127.10, 127.41, 128.03, 128.15, 129.05, 129.12, 129.40, 129.51, 129.87, 132.25, 133.56, 134.37, 135.08, 138.01; mass (CI) *m/z* calcd $C_{26}H_{24}{}^{80}Se_2$ 496.0, found 513.4 (M + 17).

1-(3-Butenyl)naphthalene (82). Use of Dianion 85.



Et$_3$BHLi (1 M in THF, 0.23 mL, 0.23 mmol) was added dropwise by syringe to a stirred solution of dibenzo[c,e][1,2]diselenin **84** (33.3 mg, 0.107 mmol) in THF (5 mL) (Ar atmosphere). At the end of the addition a colorless solution had formed. Dimesylate **81** (40.0 mg, 0.107 mmol) in THF (0.82 mL) was then injected dropwise, the solution stirred at room temperature for 18 h, and then evaporated at room temperature. Flash chromatography of the hexane-soluble portion of the residue over silica gel (2.0 x 15 cm), using hexane, gave **82** (19.6 mg, 100%), spectroscopically identical to an authentic sample,[80] and allowed recovery of dibenzo[c,e][1,2]diselenin (30.4 mg, 91%).

Bis[(2-Hydroxymethyl)phenyl] Diselenide (93)

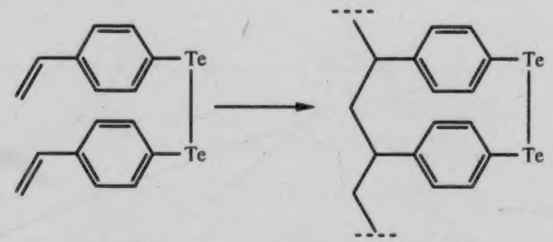


92a

93a

$LiAlH_4$ (788.2 mg, 20.77 mmol) was added in small portions to a stirred and cooled (0 °C) suspension of selenol acid **92a** (531.6 mg, 2.644 mmol) in THF (5 mL). Stirring was continued for 1 h, and water was then added dropwise. The cold bath was removed, and air was bubbled through the stirred mixture for 30 min. The mixture was extracted with CH_2Cl_2, dried ($MgSO_4$) and evaporated. Crude **93** (472.1 mg, *ca.* 1.268 mmol) had: FTIR (CH_2Cl_2 cast) 3310 (broad), 747 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.8-2.2 (br s, 2 H), 4.70 (s, 4 H), 7.1-7.7 (m, 16 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 33.4 (t'), 124.5 (s'), 128.0 (d'), 130.1 (d'), 131.3 (d'), 133.4 (d'), 137.0 (s'); exact mass *m/z* calcd for $C_{14}H_{14}O_2{}^{80}Se_2$ 373.9324, found 373.9337.

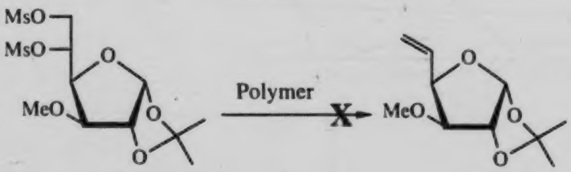
Brill's Polymer (108).


107 108

A solution of sodium dodecyl benzenesulfonate (39.1 mg, 0.112 mmol) and $B(OH)_3$ (560 mg, 9.05 mmol) in water (43 mL) (room temperature) was placed in a three-neck round-bottomed flask fitted with reflux condenser, mechanical stirrer attached to a four-blade glass propeller and a thermometer. A solution of gelatin (200 mg) in water (7 mL, 60 °C) was added. The pH of the resulting mixture was adjusted to 10.0 (litmus paper) by dropwise addition of 10% aqueous NaOH, and $NaNO_2$ (13.2 mg, 0.191 mmol) was added to the mixture. A solution of styrene (1.25 mL, 10.9 mmol), divinylbenzene (3.75 mL, 26.3 mmol), AIBN (47.5 mg, 0.289 mmol) and bis-(*p*-vinylphenyl)ditelluride (199 mg, 0.431 mmol) in PhMe (10 mL) was then added, and the mixture was stirred (400 rpm; speed measured with a stroboscope) at 80 °C for 17.5 h (Ar atmosphere). The mixture was cooled, and filtered. The resulting solid was washed successively with water, MeOH, and acetone, placed in a Soxhlet extractor, and extracted with THF for 18 h. The residue was dried under vacuum, giving polymer **108** (2.73 g, *ca.* 0.982 mmol Te) as a brittle, red-orange porous solid. Anal. C, 87.71; H, 7.70, Te 4.59.

Note: Polymer obtained by this process was flushed with oxygen free Ar prior to use.

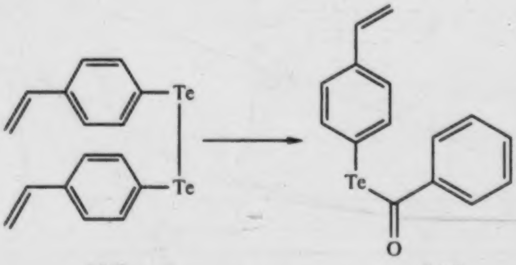
Reactions with polymer 108: General procedure.



48 **49**

A suspension of polymer **108** (244.6 mg, 15.8% Te, *ca.* 0.3029 mmol Te) in dry THF (3 mL) was stirred for 10 min at room temperature. A solution of Et_3BHLi (1M in THF, 0.8 mL, 0.8 mmol) was injected, and the mixture was stirred until the polymer had changed color from red to pale yellow (*ca.* 4 h). The polymer was washed with THF (4 x 4 mL) and suspended in freshly distilled THF (3 mL). A solution of dimesylate **48** (21.0 mg, 0.0538 mmol) in THF (3 mL) was then added and the suspension was stirred at 40 °C for 12 hours. The mixture was filtered, the solid washed with THF (4 x 4 mL) and the combined organic solutions were evaporated. Flash chromatography of the residue over silica gel (1 x 15 cm), using 1:1 EtOAc-hexane, gave only unreacted starting material (20.0 mg, 99% recovery).

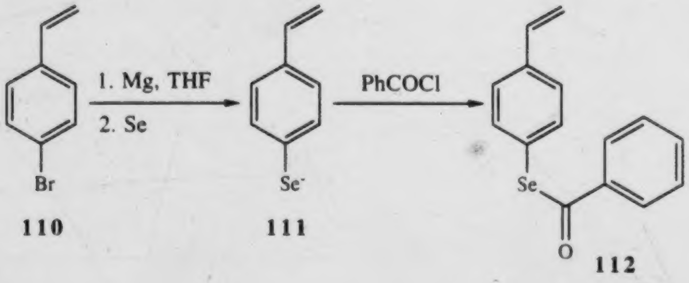
p-Vinylphenyl Tellurobenzoate (113):



107 **113**

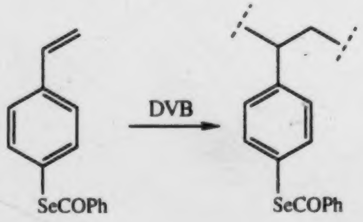
A solution of Et_3BHLi (1 M in THF, 1.0 mL, 1.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of bis(*p*-vinylphenyl)ditelluride **107** (230.7 mg, 0.5000 mmol) in THF (5.0 mL) (Ar atmosphere). PhCOCl (181.8 mg, 1.293 mmol) was added and stirring was continued at 0 °C for 30 min. The mixture was diluted with EtOAc (5 mL), and washed with water (2 x 5 mL) and brine (5 mL). Flash chromatography of the residue over silica gel (2.5 x 20 cm), using 1:9 CH_2Cl_2-petroleum ether, gave telluroester **113** (58.8 mg, *ca*. 35% yield) as a very unstable yellow oil: FTIR (CH_2Cl_2 cast) 1672 cm^{-1}; ^1H-NMR (300 MHz, $CDCl_3$) δ 5.32 (dd, *J* = 11.0, 1.0 Hz, 1 H), 5.82 (dd, *J* = 17.5, 1.0 Hz, 1 H), 6.75 (dd, *J* = 17.5, 11.0 Hz, 1 H), 7.45-7.55 (m, 9 H); ^{13}C-NMR (75.5 MHz, $CDCl_3$) δ 115.11 (t'), 127.08 (s'), 127.42 (d'), 129.20 (d'), 134.09 (d'), 136.13 (d'), 137.75 (d'), 140.60 (s'), 142.73 (s'), 196.37 (s') (two signals overlap), exact mass *m/z* calcd for $C_{15}H_{12}O^{130}Te$ 337.9950, found 337.9951.

p-Vinylphenyl Selenobenzoate (112):



p-Bromostyrene (4.00 g, 28.4 mmol) in THF (65 mL) was added dropwise over 35 min to a stirred suspension of I_2-activated Mg (860 mg, 27.5 mmol) in THF (5 mL) at room temperature (Ar atmosphere). The mixture was refluxed until all the Mg had been consumed (1 h), and then cooled (0 °C). Se powder (2.20 g, 27.9 mmol, 200 mesh) was added and the mixture stirred until most of the Se had reacted (*ca.* 30 min). PhCOCl (4.00 g, 28.4 mmol) was added and the orange mixture was stirred at 0 °C for 2 h. The resulting solution was dissolved in EtOAc (100 mL), washed with water (2 x 30 mL) and brine (20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (6 x 18 cm), using 1:4 CH_2Cl_2-petroleum ether, gave selenoester **112** (5.74 g, 73% yield) as yellow crystals: mp 132 °C (decomposes); FTIR (CH_2Cl_2 cast) 1681 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.33 (dd, J = 9.9, 0.9 Hz, 1 H), 5.82 (dd, J = 16.2, 0.9 Hz, 1 H), 6.75 (dd, J = 9.9, 16.2 Hz, 1 H), 7.50-7.60 (m, 7 H), 7.90-8.00 (m, 2 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 115.16 (t'), 125.09 (s'), 127.18 (d'), 127.39 (d'), 128.99 (d'), 133.93 (d'), 136.26 (d'), 136.47 (d'), 138.43 (s'), 138.58 (s'), 193.38 (s'); exact mass *m/z* calcd for $C_{15}H_{12}O^{80}Se$ 288.0053, found 288.0057.

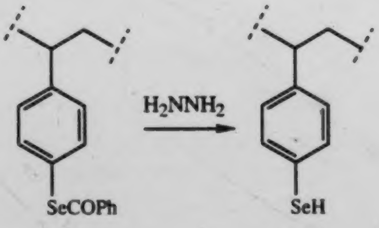
Poly(selenoester) (114).



112 **114**

A solution of selenoester **112** (1.00 g, 3.48 mmol) and AIBN (30.0 mg, 0.183 mmol) in divinylbenzene (2.41 mL, 9.29 mmol) (Ar atmosphere) was stirred at 100 °C for *ca.* 30 min. Heating was continued for 1.5 h and the resulting solid was extracted with THF in a Soxhlet extractor for 6 h. The residue was dried under vacuum, giving polymer **114** (2.06 g, *ca.* 3.48 mmol Se) as a yellow solid insoluble in THF and diethyl ether: FTIR 1675 cm^{-1}.

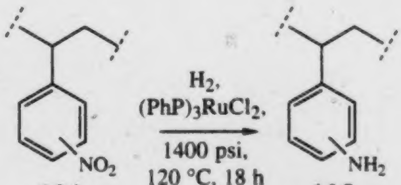
Poly(selenol) (115).



114 **115**

NH_2NH_2 (0.10 mL, 3.2 mmol) was added to a stirred suspension of polymer **114** (1.00 g, *ca*. 1.69 mmol Se) in THF (1 mL) at room temperature. After 2 h, 10% aqueous hydrochloric acid (10 mL) was added dropwise to the mixture. The suspension was filtered, washed successively with water and MeOH, placed in a Soxhlet extractor and extracted with THF for 6 h. The residue was dried under vacuum, and gave polymer **115** (614 mg, *ca*. 1.45 mmol Se) as an orange solid: FTIR no absorption in the C=O region. Anal. C, 74.41; H, 6 88, Se, 18.71.

Hydrogenation of poly(nitrostyrene) (105).



104 **105**

Poly(nitrostyrene) (**104**) (11.4 g) was suspended in a solution of $RuCl_2(PPh_3)_3$ (1.20 g, 1.25 mmol) in 1:1 (v/v) EtOH-PhH (35 mL). The mixture was placed in an autoclave under H_2 (80 atm) at 120 °C for 24 h. The suspension was then filtered and the dark-colored polymer was washed successively with EtOH, THF, THF-H_2O (5:1) and acetone. The residue was dried under vacuum, and gave polymer **105** (10.0 g) as a dark green solid: FTIR 3427 cm^{-1}. Anal. C, 59.424; H, 5.441; N, 13.360.

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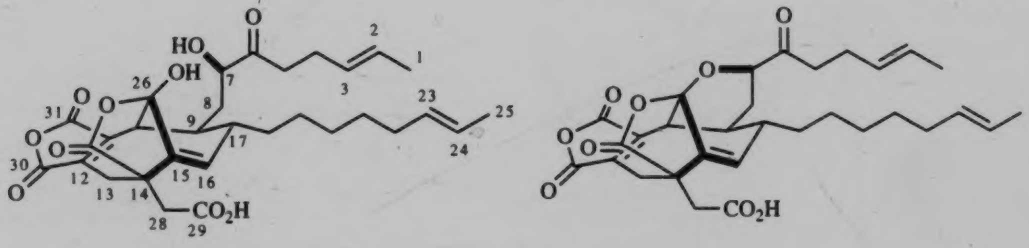
PART II

Synthetic Studies on the Farnesyl Transferase Inhibitors CP-225,917 and CP-263,114.

I. Introduction.

While screening for inhibitors of squalene synthase and Ras farnesyl transferase (FTase), chemists at Pfizer Central Research isolated from the fermentation broth of an unidentified fungus, two structurally unique compounds, CP-225,917 and CP-263,114 (Figure 1).[1,2] The compounds are characterized by a bicyclo[4.3.1]deca-1,6-diene core and two extended alkyl chains.

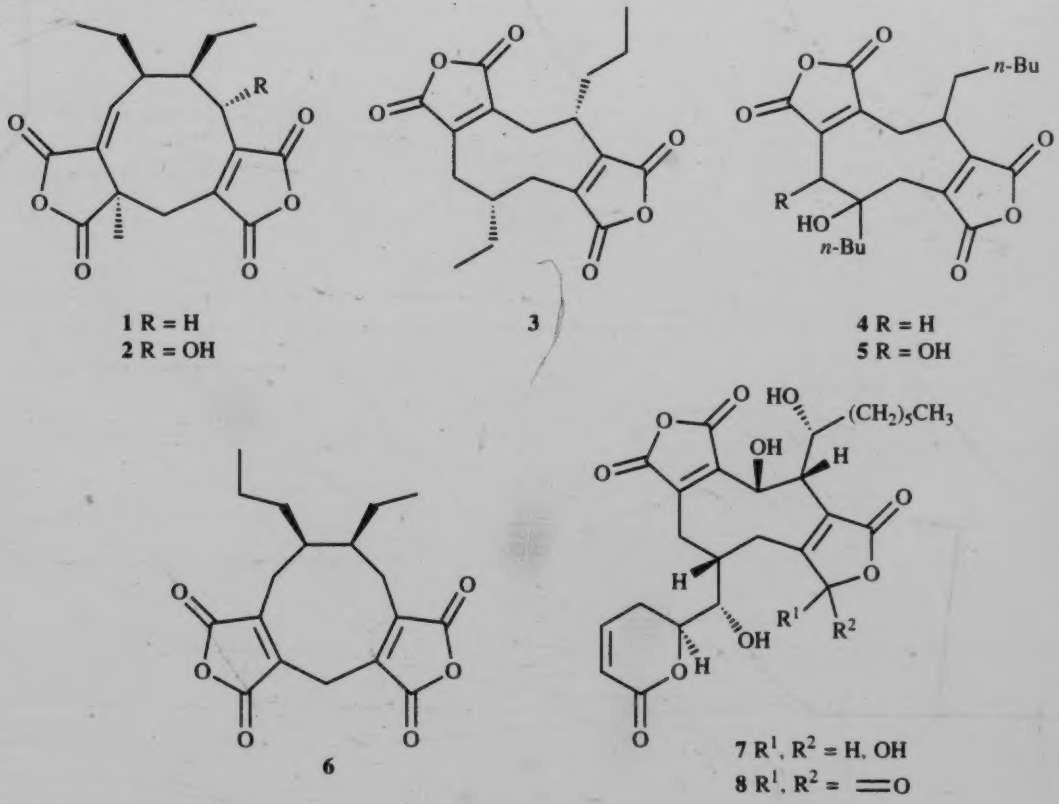


CP-225,917

CP-263,114

Figure 1 *Structures of the fungal metabolites isolated by chemists from Pfizer.*

The proposed biosynthetic origin[2] of CP-225,917 and CP-263,114 relates the compounds to the nonadrides,[3] an unusual class of mold metabolites which are characterized by the presence *inter alia* of a substituted nine-membered ring fused to two five-membered anhydride units. The nonadrides include glaucanic acid (**1**),[4] glauconic acid (**2**),[3] byssochlamic acid (**3**),[4] scytalidic acid (**4**),[5] castaneiolide (**5**),[6] heveadride (**6**),[7] and rubratoxins A (**7**) and B (**8**) (Figure 2).[8]



1 R = H
2 R = OH

3

4 R = H
5 R = OH

6

7 R^1, R^2 = H, OH
8 R^1, R^2 = =O

Figure 2 *Structure of several nonadrides.*

Although CP-225,917 and CP-263,114 were not good squalene synthase inhibitors (IC_{50} values of 43 μM and 320 μM, respectively), both inhibited FTase activity with IC_{50} values of 6 μM. CP-225,917 and CP-263,114 belong to an emerging group of natural products that are FTase inhibitors,[9] and these substances are under intense investigation.

Two topics are relevant in the review section for my work on the synthesis of CP-225,917: the biological basis of the importance of the compound, and the use of anionic oxy-Cope rearrangement, which was our strategy used to build the carbobicyclic core of the natural product.

A. Biological activity of CP-225,917.

Cell-growth is a carefully regulated process. Occasionally, however, the mechanisms that control cell proliferation fail. A cell may undergo genetic and morphological transformations which lead to such anomalous processes and to abnormal interactions with neighboring cells. The descendants of this malfunctioning cell, inheriting its ability to grow in a manner that is unresponsive to regulation, generate a localized mass of cells – a tumor. These tumors may ultimately invade the surrounding tissue, a process known as malignancy, and eventually reach the blood vessels, spreading to areas far away from the original site of formation. This spreading is called metastasis. The devastating effects of cancer are, of course, well known, and research on prevention, control and cure is an immensely important topic in medicinal chemistry.

1. The Nature of Oncogenes.

Our knowledge of the causes and mechanisms of cell transformations associated with malignant tumors is still fairly limited and is generally based on models that do not fully represent the complexity of real human tumors.[10] However, it has been established that certain altered cellular genes, whose products are involved either in transforming cells in culture or in inducing cancer in animals, also play an important role in human cancers.[11] Named oncogenes (from the Greek *onkos*, bulk or mass), these mutated genes are similar to their normal counterparts (proto-oncogenes) that act on growth control pathways basic to animal life.

2. Proteins Encoded by Proto-Oncogenes and Oncogenes.

The proteins responsible for control of cell-growth are encoded by four classes of proto-oncogenes: growth factors (Class I proto-oncogenes), growth factor receptors (Class II), intracellular signal transducers (Class III), and nuclear transcription factors (Class IV).[12] These proteins trigger a wide range of cell responses that are intimately related to each other: the growth of cells either in culture or in animals – a process induced by specific *growth factors* – is sensitive to the tenancy of *growth factor receptors*. *Intracellular signal transducers* (second messengers) are stimulated by these receptors and precipitate a cascade that will ultimately relay the growth signal to *transcription* *factors* present in the cell nucleus. It is the transcriptional response that changes the protein composition of the cell, affording the necessary building blocks that will effect cell growth.

Of all classes of proto-oncogenes, Class III (intracellular signal transducers) is the largest,[12] and comprises the *ras* genes. The *ras* gene products, a family of 21-kDa proteins, called p21 or Ras,[10,13] play a key role in cell growth and are closely associated with 30% of all human cancers.[14]

3. The Role of Normal Ras Proteins.[15]

Optimal division and differentiation in many cells requires the synthesis of normal Ras.[10,13] Ras, and other cell membrane proteins belonging to the same class, are found *within* the cell, anchored to the inner face of the plasma membrane.

The several steps of the Ras cycle in the cell are as follows. As a growth factor binds to a receptor tyrosine kinase, the conversion between inactive GDP-bound Ras to active GTP-bound Ras is triggered. The protein kinase Raf then binds to the active Ras-GTP complex, and the now active Raf initiates a phosphorylation cascade that transmits a proliferative signal to the nucleus.[16] This process, however, is *totally dependent* on the membrane localization of Ras.

4. Membrane Localization of Ras.

It was not until 1984 that it was determined that labeled mevalonate was covalently incorporated into several cell proteins.[17] Shortly thereafter, a farnesyl group, a C_{15}-isoprenoid unit, was identified as being one of the products derived from mevalonate that is incorporated post-translationally into certain proteins, including Ras.[18]

Post-translational prenylation is performed by enzymes able to recognize certain amino acid sequences of the protein, the so-called CaaX motifs.[16] This short sequence is composed of a cysteine residue (C), followed in general by two aliphatic (a) amino acids and one carboxy-terminal aminoacid (X). The nature of aminoacid X may vary, and this determines which transferase will bind the protein. In the case of Ras, this enzyme is a farnesyl transferase (FTase).

The lipophilic farnesyl group, covalently attached to Ras, is responsible for membrane localization of the protein, by interacting with the lipids that constitute the inner side of the cell membrane.

5. The Connection Between Mutant *ras* Genes and Cancer.

In malignant cells, some of the commonest mutations are alterations of the Harvey (Ha-), Kirsten (Ki-) or N-*ras* genes.[14,19,20] These alterations have been found in 50% of colon cancers;[21] in carcinomas of lung[22] and pancreas;[23] and various leukemias.[24]

The transformation of the normal *ras* proto-oncogene into a *ras* oncogene can be triggered by carcinogens or oncogenic viruses; the *ras* oncogene then codes for the synthesis of a mutant oncogenic Ras protein.[13] The most common mutation of the *ras* genes in human cancer cells produces Ras proteins that lack GTPase activity,[25] the fundamental process that turns the cell-growth mechanism off – by converting an active GTP-Ras complex into an inactive GDP-Ras complex. The membrane-bound mutant protein, permanently activated, continuously generates proliferation signals,[10] thus leading to cancer.

6. The Importance of FTase Inhibition.

From the above summary, it is clear that one way of dealing with the unregulated cell-growth mechanism is to prevent membrane attachment of mutant Ras protein. This can be achieved by inhibiting the post-translational farnesylation step, because this action would render the mutant protein unable to be anchored to the cell membrane. Consequently, the proliferation cascade would not be triggered.

Current work in the area of farnesyl transferase inhibition provides support for the above idea.[26,27] It has been shown that the growth of malignant cells can be inhibited by FTase inhibitors *in vitro*,[28] and *in vivo* experiments[29] have also shown that certain tumors can completely regress. *An important observation was made that the growth of normal cells was not affected*, a fact that is remarkable, since the inhibitors are not Ras-specific.[16,26]

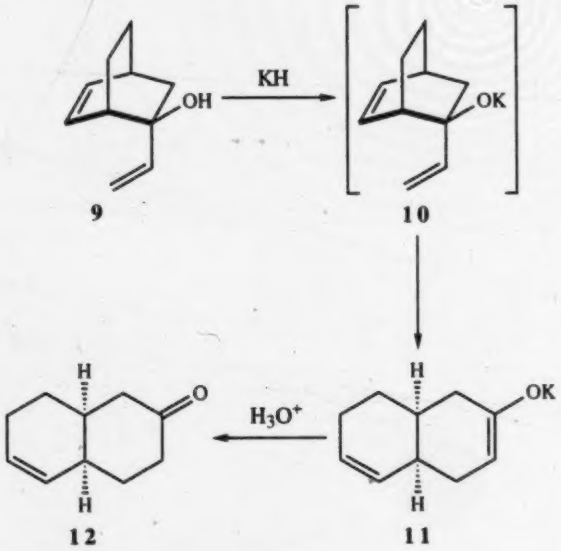
This unprecedented selectivity, along with the impressive in vitro and in vivo performance of some FTase inhibitors, indicates that research in this area is of great importance for the development of new chemotherapeutics for cancer.

CP-225,917 is a Ras protein farnesyl transferase inhibitor, although its mode of action, and what features confer inhibitory properties are unknown. One might speculate, however, that the anhydride substructure serves as a prodrug that is converted into a dicarboxylic acid on hydrolysis. Chaetomelic acids,[9b,c] which are also inhibitors of FTase, are believed to follow this pattern. The hydrocarbon appendages may mimic the farnesyl unit that becomes attached to the Ras protein, and suggests that the hydrocarbon chains of CP-225,917 may be important, although those present in the natural product may not be optimal.

No synthetic route to CP-225,917 is available. The present work, therefore, may provide the tools necessary for the design of novel anticancer drugs based on the properties and features of the natural product.

B. Anionic Oxy-Cope Rearrangement.[30]

In 1975, Evans and Golob[31] reported that oxy-Cope [3,3]-sigmatropic rearrangements underwent an appreciable increase in rate upon conversion of the starting alcohol (e.g., **9**) into the potassium alkoxide (e.g., **10**) (Scheme 1). Rate acceleration by factors of up to 10^{17} were observed, compared to the thermal process.



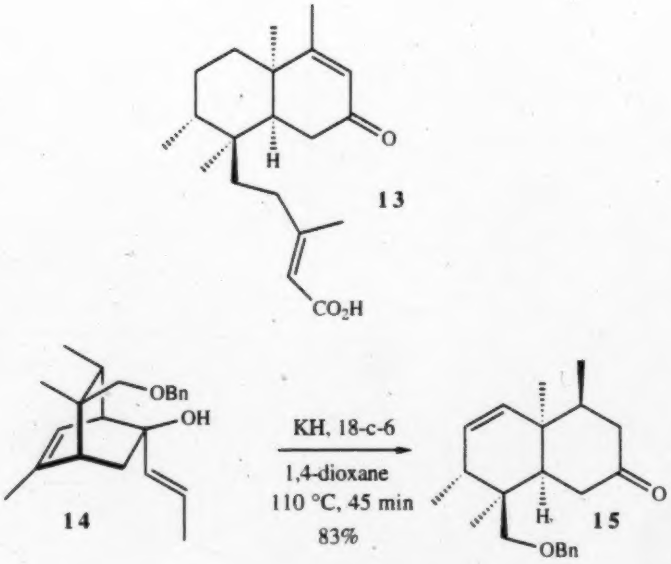
Scheme 1

It was also observed that the increase in rate is directly related to the extent of alkoxide-metal dissociation; consequently, addition of 18-crown-6 (a K^+ ionophore) to the reaction mixture accelerates the rearrangement. These developments made the anionic oxy-Cope rearrangement a prominent technique in organic synthesis.[32]

Since this topic constitutes a very active area of research and has become central to our synthetic studies, it is useful to outline the most recent developments in the field. The literature from 1995 to the present is covered, although not exhaustively, since a very thorough review has appeared recently in the literature.[30]

1. Use of Anionic oxy-Cope Rearrangement in the Total Synthesis of Natural Products.

The anionic oxy-Cope rearrangement has been used as the key step in the synthesis of several natural products. For instance, in the synthesis[33] of (±)-*cis*-clerodane diterpenic acid **13** (Scheme 2), the *cis*-decalin **15** was arrived at by rearrangement of the bicyclo[2.2.2]octene **14**, in good yield.


H
O
CO₂H
OBn
OH
KH, 18-c-6
1,4-dioxane
110 °C, 45 min
83%
H
O
OBn

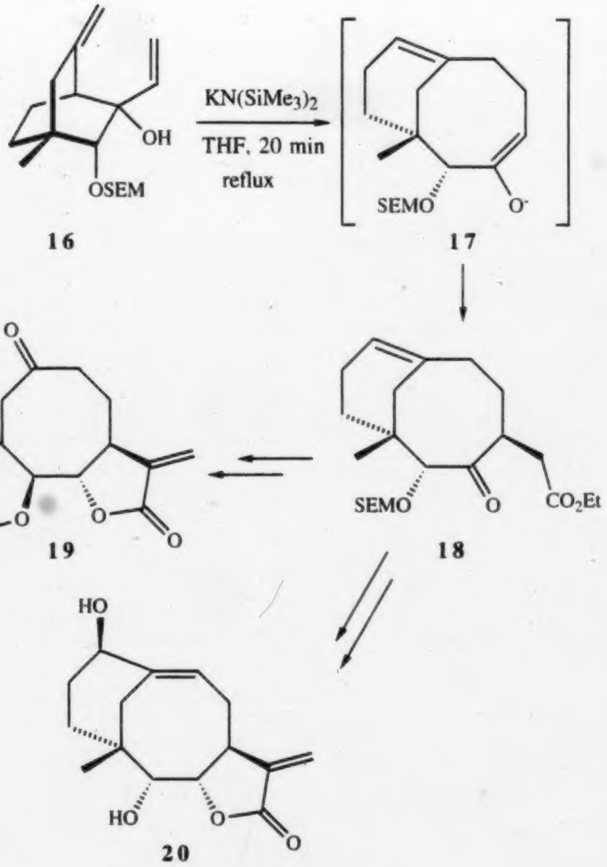
13

14

15

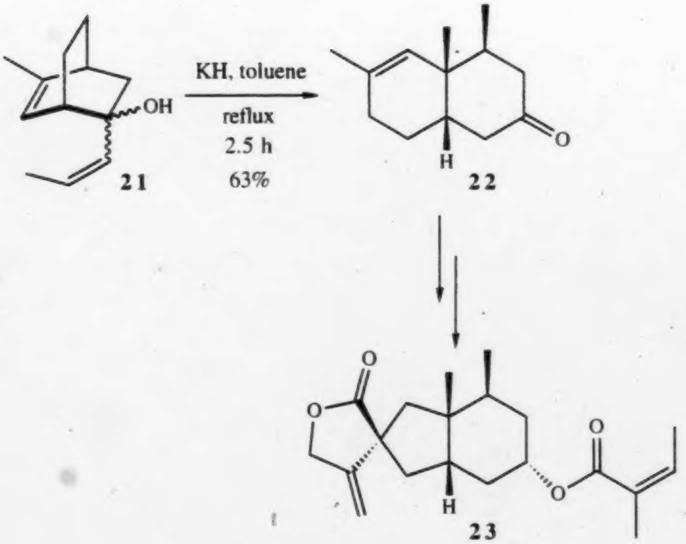
Scheme 2

In the synthesis of cyclooctanoid natural products, the asymmetric synthesis of sesquiterpene lactones **19** (vulgarolide) and **20** (deoxocrispolide) has been described[34] from the common intermediate **18**. This compound was prepared in one step from optically active **16** by an anionic oxy-Cope rearrangement, followed by *in situ* trapping of the resulting enolate anion **17** (Scheme 3).


KN(SiMe3)2
THF, 20 min
reflux
OH
OSEM
SEMO
O-
CO2Et
HO
16
17
18
19
20

Scheme 3

The bakkenolide sesquiterpene (-)-homogynolide A (**23**) was also prepared by using an anionic oxy-Cope rearrangement as the key step (Scheme 4).[35] In this synthesis, rearrangement of an inseparable mixture of optically active *endo*- and *exo*-isomers **21** leads to *cis*-decalin **22** in 63% yield (based on recovered unreacted *exo* starting material). Ring contraction (ozonolysis followed by aldol condensation) gave the *cis*-fused bicyclo[2.3.0]nonane carbocyclic framework.

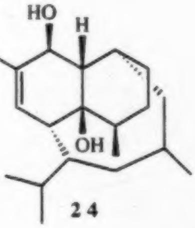


Scheme 4

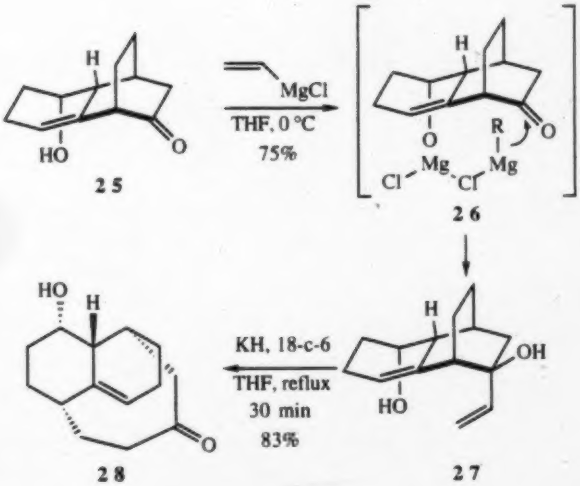
There is a great deal of ongoing research towards the synthesis of several natural products *via* anionic oxy-Cope rearrangement, as well as towards the generation of specific ring systems. For purposes of discussion, these works are divided into two categories: *Approaches to the Total Synthesis of Natural Products* and *Synthesis of Carbocyclic Frameworks*. The work of the Paquette group on dianionic oxy-Cope rearrangement of squarate ester derivatives, leading to polyquinanes,[36] seems of lesser relevance to our own studies and has, accordingly, been omitted from the following discussion.

2. Approaches to the Total Synthesis of Natural Products.

The first synthesis of a compound representing the functionalized tricyclic framework of vinigrol (**24**) was reported recently.[37] The approach involved rearrangement of alcohol **27** into cyclooctanoid **28** (Scheme 5). The required allylic alcohol was generated by exposure of hydroxy ketone **25** to vinyl magnesium chloride; the high stereoselectivity observed was understandable on the basis of chelation control by the remote hydroxyl group (*cf.* **26**→**27**, Scheme 5).

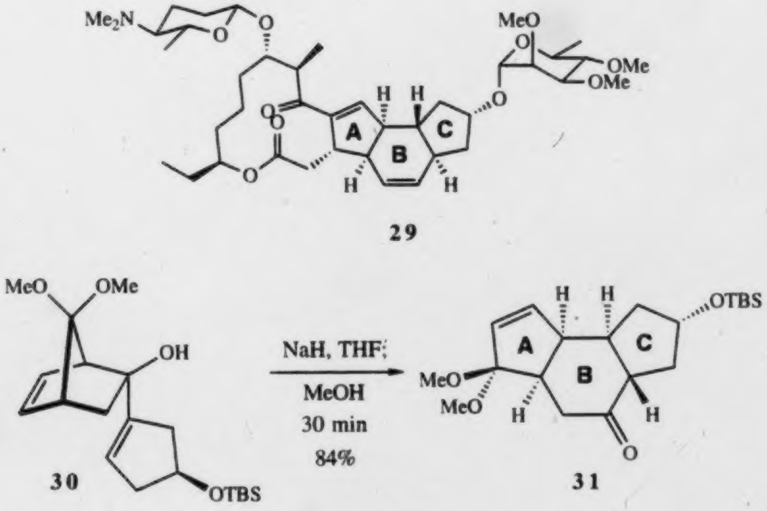


24


H
HO
O
25
MgCl
THF, 0 °C
75%
H
O
R
O
Cl
Mg
Cl
Mg
26
H
OH
HO
27
KH, 18-c-6
THF, reflux
30 min
83%
HO
H
O
28

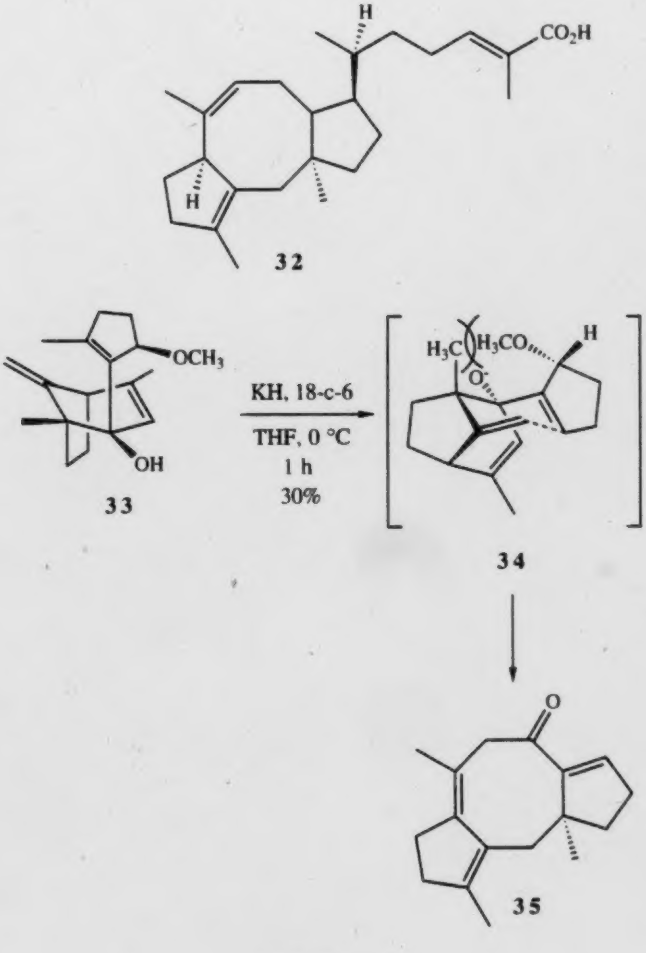
Scheme 5

In synthetic studies on (-)-spinosyn A (*cf.* **29**, Scheme 6), the preparation of optically active tricyclic compound **31** was reported[38] by rearrangement of alcohol **30**. This, in turn was prepared by 1,2-addition of an optically active lithiated cyclopentenone derivative to an optically active bicyclo-[2.2.1]heptenone. Further manipulation of **31** gave an advanced intermediate representing the non-macrolide portion of **29**. The absolute configuration of the B/C ring junction of **31** is opposite to that eventually required, but this was intentionally arranged in order to accommodate subsequent steps. Eventually, the correct stereochemistry was restored.



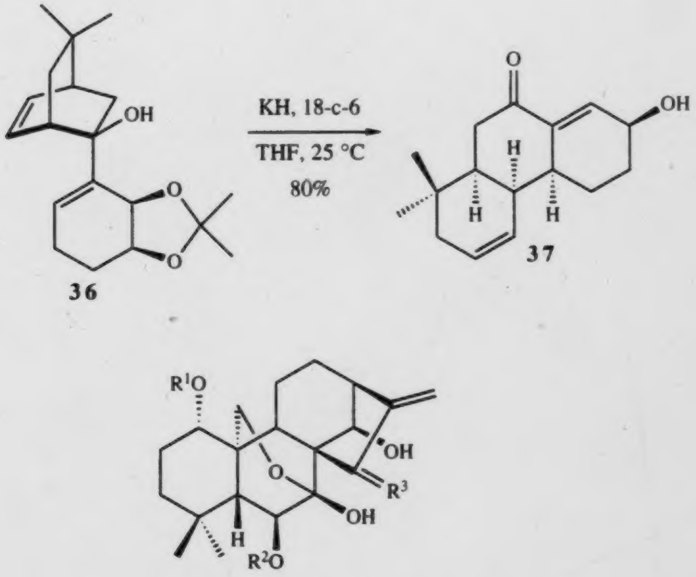
Scheme 6

The Paquette group has also described an approach[39] to the carbocyclic skeleton of albolic acid (**32**) (a member of the ceroplastin sesterterpene class) based on the rearrangement shown in Scheme 7. However, this route gave a very low overall yield (due to, *inter alia*, unfavorable steric interactions in the transition state leading to the product; *cf*. Scheme 7, **34**). In addition, the initial product underwent an undesired deconjugation of the double bond initially formed.


H
CO2H
H
32
OCH3
OH
33
KH, 18-c-6
THF, 0 °C
1 h
30%
H3C
H3CO
H
O
34
O
35

Scheme 7

The synthesis of optically pure tricyclic compound **37** by a route based on oxy-Cope rearrangement, followed by β elimination (Scheme 8), has been reported.[40] Compound **37** was then elaborated into an advanced intermediate *en route* to the kaurane diterpenoids rabdokaurin C (**38**) and oridorin (**39**).

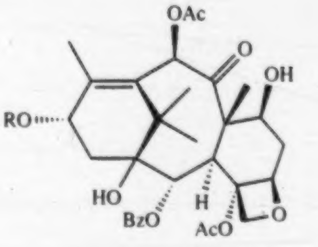

OH
KH, 18-c-6
THF, 25 °C
80%
O
O
36
O
OH
H
H
H
37
R¹O
OH
O
R³
OH
H
R²O

38 $R^1 = R^2 = Ac, R^3 = H, -OH$

39 $R^1 = R^2 = H, R^3 = O$

Scheme 8

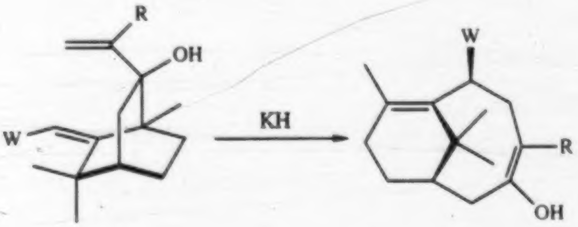
The anionic oxy-Cope rearrangement has also been applied in entries to the carbon framework of taxol (**40**).



R = COCH(OH)CHPhNHCOPh

40

In the approach of Martin *et al.*[41] compounds of general structure **41** (Scheme 9) were prepared and, upon treatment with KH, give rise to bicyclo[5.3.1]undec-7-enes **42**.



41

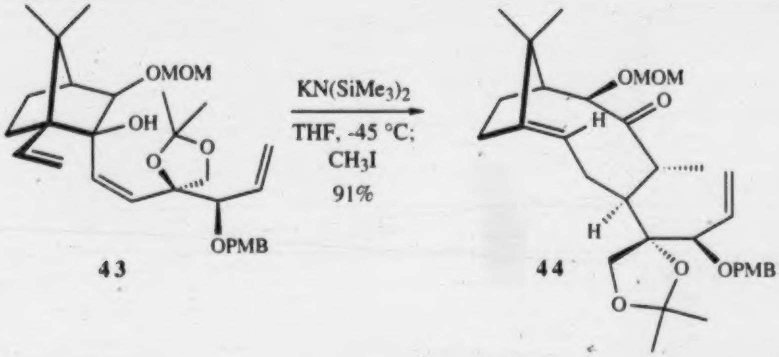
W = H, OR, SR

R = H

42

Scheme 9

An alternative approach[42] to the taxol framework leads to the highly functionalized bicyclo[6.2.1]undecene **44** (Scheme 10), and relies on a bond migration later in the synthesis to generate the appropriate [5.3.1]-bicyclic framework.

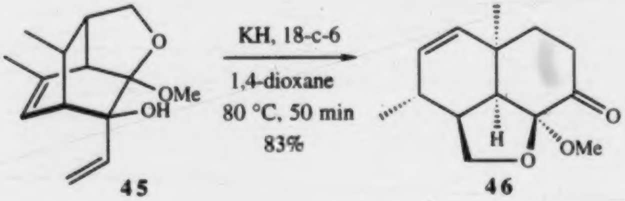

OMOM
OH
O
O
OPMB
KN(SiMe$_3$)$_2$
THF, -45 °C;
CH$_3$I
91%
OMOM
O
H
H
O
O
OPMB

43 **44**

Scheme 10

3. Synthesis of Carbocyclic Frameworks.

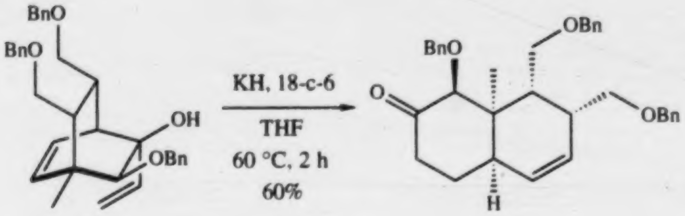
Anionic oxy-Cope rearrangement offers a convenient entry to decalin systems, as shown in the synthesis of **13**[33] (*vide supra*), and bakkenolide **23** *via* decalin **22** (*vide supra*).[35] In synthetic studies towards **13**,[43] several polycyclic decalin derivatives such as **46** were also prepared (Scheme 11).


O
OMe
OH
KH, 18-c-6
1,4-dioxane
80 °C, 50 min
83%
O
H
O
OMe

45 **46**

Scheme 11

cis-Decalins have been made enantiospecifically by converting optically pure *cis*-1,2-dihydrocatechols into the required 3-hydroxyl-1,5-diene system, followed by rearrangement, as in the conversion of **47** into **48** (Scheme 12).[44]

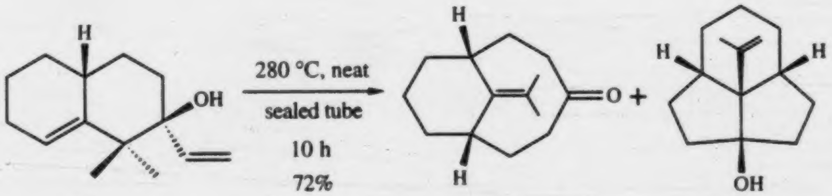

BnO
BnO
OH
OBn
KH, 18-c-6
THF
60 °C, 2 h
60%
BnO
O
OBn
OBn
H

47 **48**

Scheme 12

4. Thermal oxy-Cope Rearrangements in Cases where the Anionic Version was Unsuccessful.

In a few cases, the rate acceleration normally associated with the anionic oxy-Cope rearrangement was not observed, although the process could be carried out thermally. Thus, bicyclo[4.4.0]decane **49** could be converted into bicyclo[5.3.1]undecane **50** by heating at 280 °C in a sealed tube (Scheme 13); compound **50** was obtained along with the transannular ene product **51**.[45]


H
OH
280 °C, neat
sealed tube
10 h
72%
H
H
O +
H
H
OH

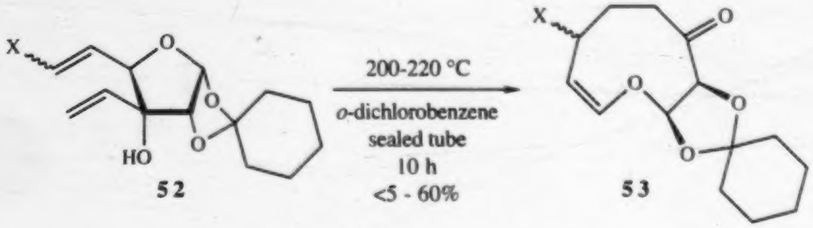
49 **50** **51**

2 : 1

Scheme 13

In contrast, treatment of **49** with base gave a complex mixture.

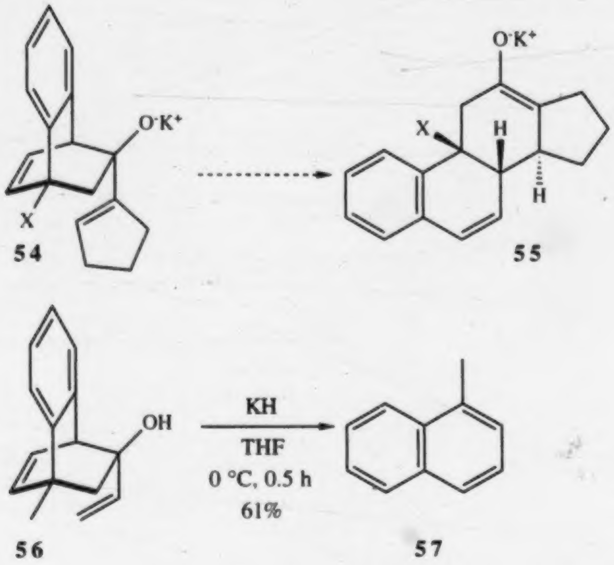
The anionic process was also of no avail in the rearrangement of sugar derivatives **52** into medium ring ethers **53**, which were arrived at by the thermal variant of the reaction (Scheme 14).[46] The use of base only led to recovery of starting material (**52**).



X = H, Z-CO_2Et, E-CO_2Et, Z-$COCH_3$, E-$COCH_3$, Z-CN, E-CN

Scheme 14

Finally, bicyclo[2.2.2]octene **56**,[47] which was used as a test case for potential precursors to optically pure analogs of A-ring aromatic steroids (*cf.* Scheme 15, **54**→**55**), was examined. Upon treatment with KH in THF it affords 1-methylnaphthalene (**57**) as the only cyclic product, a result of a competing oxy-ionic retro-Diels–Alder reaction.[48] The authors, however, did not mention whether the transformation could be carried out thermally.

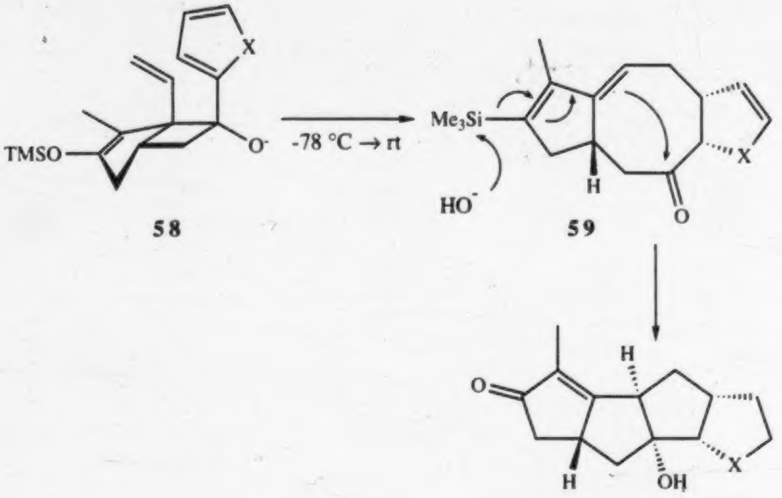


Scheme 15

There are, of course, other examples[49] in the literature where no mention is made of any attempts at performing the oxy-Cope rearrangement other than under thermal conditions; these cases are not discussed here.

5. Tandem Reactions Involving Anionic Oxy-Cope Rearrangement.

Often, the rearranged product can lead to complex polycyclic products with little extra manipulation. For example, alkoxide **58**, in which one of the unsaturations of the required 3-hydroxyl-1,5-diene system belongs to an aromatic ring, smoothly rearranges into tricyclic ketone **59** (Scheme 16).[50] Hydrolytic desilylation of **59** during work-up



58 **59** **60** X = O, S; 60%

Scheme 16

affords the linearly fused tetracyclic compound **60**. The involvement of the aromatic ring in the oxy-Cope rearrangement is possible owing to the exothermic nature of the ring expansion process, which releases the strain of the [3.2.0]-bicyclic system. Carbocyclic aromatic moieties can also participate in this anionic oxy-Cope process.[50]

There have also been reports of tandem Zr-catalyzed *o*-phenol oxygenation–oxy-Cope rearrangement,[51] and tandem [2,3]-Wittig–oxy-Cope rearrangement.[52] Since these processes lead to linear, acyclic compounds, they will not be discussed.

II. Results and Discussion.

The intricate structure of CP-225,917 offers many opportunities for synthetic organic chemists to develop and apply new strategies, and it is not at all clear how the compound will eventually be reached by total synthesis. All that is certain is that the substance represents an irresistible target.

1. Radical Cyclization - First generation.

Our initial approach to the carbocyclic core of CP-225,917 was based on the disconnection shown in Figure 3. The goal was to determine if a [6.4.0]-bicyclic species such as **61** could be converted into compound **62** by means of radical cyclization (Scheme 17).

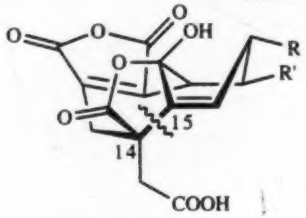
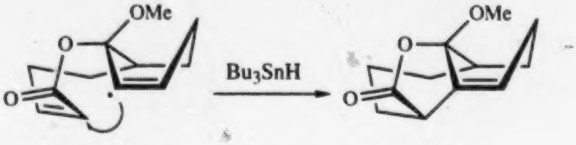


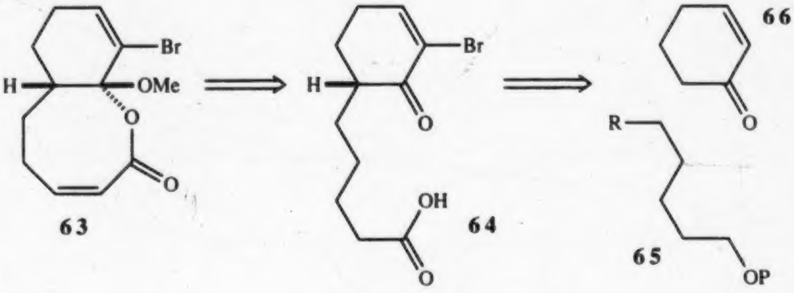
Figure 3 *Our first approach to the carbobicyclic substructure of CP-225,917: disconnection between C(14) and C(15).*[53]



61 62

Scheme 17

Based on this strategy, we decided to prepare the lactone acetal **63**, which is suitably functionalized for the task in hand (Scheme 18).

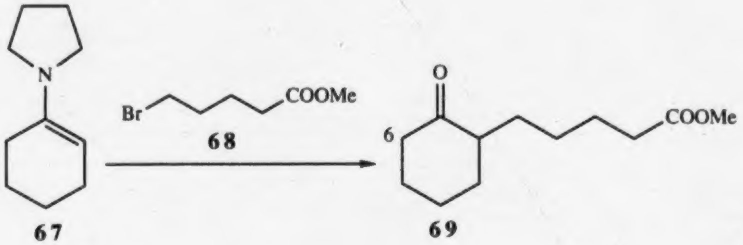


63 64 65 66

Scheme 18

Lactone acetal **63** would be formed by cyclization involving a carboxylic acid and a ketone (*cf.* **64**, Scheme 18) and a second double bond would then be introduced α to the resulting lactone carbonyl by selenoxide elimination. We expected that the bromo enone moiety of **64** could be constructed from an existing conjugated double bond by bromination followed by dehydrobromination. The five-carbon chain **65** (R = leaving group) would be attached to 2-cyclohexen-1-one (**66**) by alkylation; the required carboxylic acid could be introduced in the form of a protected alcohol, as implied in Scheme 18 (P = protecting group), or as an ester, depending on the choice of the alkylation method.

We began our work by the successful but low yielding enamine alkylation shown in Scheme 19.[54] Starting from readily prepared 1-pyrrolidino-1-cyclohexene[55] (**67**) and commercially available methyl 5-bromovalerate (**68**), the ketoester **69** was obtained in 22% yield. In addition to the disappointingly low yield, attempts to selectively introduce a double bond at C(6) of compound **69** (by reaction of the corresponding enamine with PhSeCl, followed by selenoxide elimination) were unfruitful, since we did not succeed in preparing the desired enamine; the reagents and conditions we tested are summarized in Table 1.



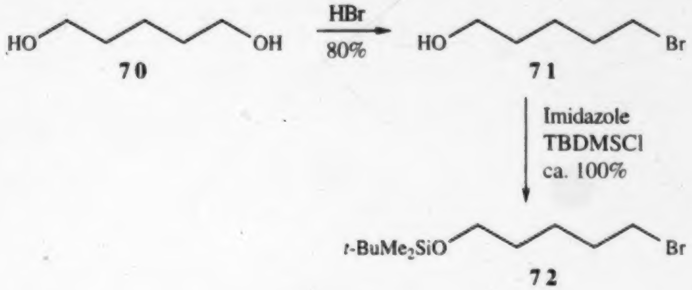
Scheme 19

Reagents and Conditions	**Reference**
pyrrolidine, refluxing PhMe, PhSeCl.	N/A
pyrrolidine, 4Å molecular sieves, TsOH, refluxing PhMe.	56
pyrrolidine, $TiCl_4$, PhMe, 80 °C.	57

Table 1 - *Attempted introduction of a double bond at C(6) of compound **69**.*

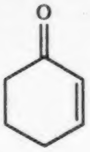
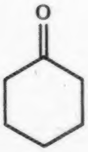
It was clear that ketoester **69** was not ideally suited for the required transformation, and so we shifted our attention to other ways of building the desired lactone acetal **63**.

According to Scheme 18, another suitable five-carbon alkylating agent should bear a leaving group at one terminus and a protected alcohol (instead of an ester) at the other. Bromide **72**[58] was prepared for this purpose, from commercially available 1,5-pentanediol (**70**), by monobromination followed by silylation (Scheme 20).[59]


HBr
80%
HO
OH
70
HO
Br
71
Imidazole
TBDMSCl
ca. 100%
t-BuMe2SiO
Br
72

Scheme 20

Attempted alkylation of a variety of substrates with bromide **72**, under several reaction conditions, are summarized in Table 2. Nevertheless, on no occasion could we isolate the desired alkylation product.

Compound	**Reagents and Conditions**	**Reference**
 **66**	a. LDA, THF, -78 °C, then **72**. b. LDA, THF, -78 °C, then the crude product obtained from the reaction of **72** with NaI in acetone at rt.	60
 **73**	KH, THF, rt, then **72**.	61

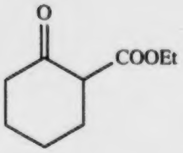
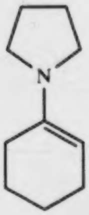
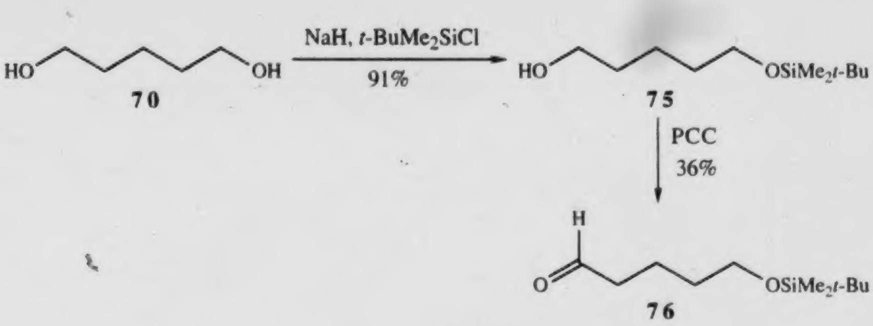
 **74**	a. i. NaH, THF, rt; ii. BuLi, THF, rt; then **72** at 0 °C.	62
	b. NaH, PhH, HMPA; then **72**.	63
 **67**	**72**, in refluxing PhMe.	55

Table 2 - *Conditions for attempted alkylation of several compounds with bromide* ***72****.*

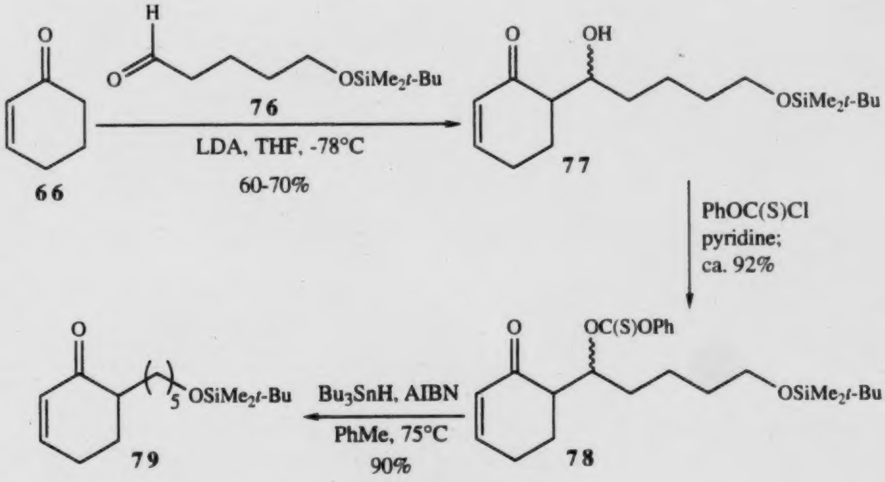
Due to the poor performance of the alkylation reactions, we found it necessary to devise an alternative route that would allow us to gain entry to compounds such as **64** (*cf.* Scheme 18). The possibility of using aldol condensation to introduce the side chain onto a suitably functionalized six-membered ring seemed very attractive.

Aldehyde **76**^{65} (Scheme 21) was prepared with this approach in mind, by selective monosilylation of commercially available 1,5-pentanediol (**70**),^{64} followed by PCC oxidation of the resulting alcohol **75**.^{65}


HO
OH
70
NaH, t-BuMe$_2$SiCl
91%
HO
OSiMe$_2$$t$-Bu
75
PCC
36%
H
O
OSiMe$_2$$t$-Bu
76

Scheme 21

Aldol condensation of aldehyde **76** with 2-cyclohexen-1-one[66] (**66**) (Scheme 22) was uneventful, and gave alcohol **77** in good yield, as a mixture of diastereomers, which were not separated.

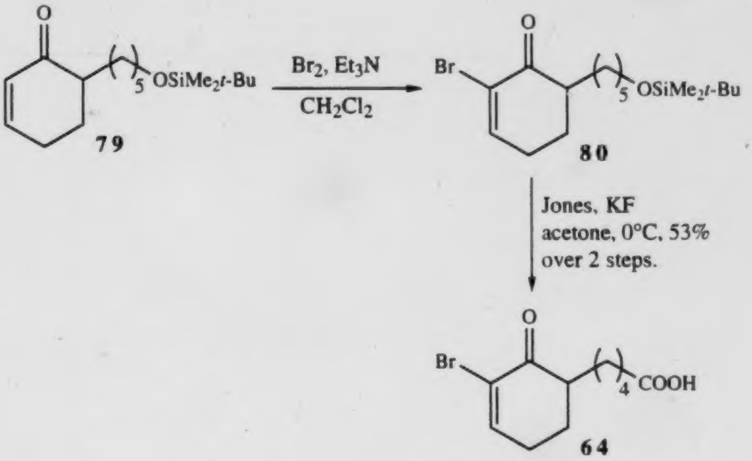

O
H
O
OSiMe$_2$$t$-Bu
76
LDA, THF, -78°C
60-70%
66
O
OH
OSiMe$_2$$t$-Bu
77
PhOC(S)Cl
pyridine;
ca. 92%
O
OC(S)OPh
OSiMe$_2$$t$-Bu
78
Bu$_3$SnH, AIBN
PhMe, 75°C
90%
O
5
OSiMe$_2$$t$-Bu
79

Scheme 22

Alcohol **77** was then deoxygenated using the modification of Barton's deoxygenation introduced by Robins[67] (*cf.* Scheme 22,

77→**78**→**79**). Cyclohexenone **79** contains the desired five-carbon side chain.

A short sequence, performed without isolation of the intermediate, and involving bromination-dehydrobromination of cyclohexenone **79**,[68] followed by oxidative cleavage of the silyl ether **80**,[69] gave bromo acid **64** in 53% yield over two steps from **79** (Scheme 23).

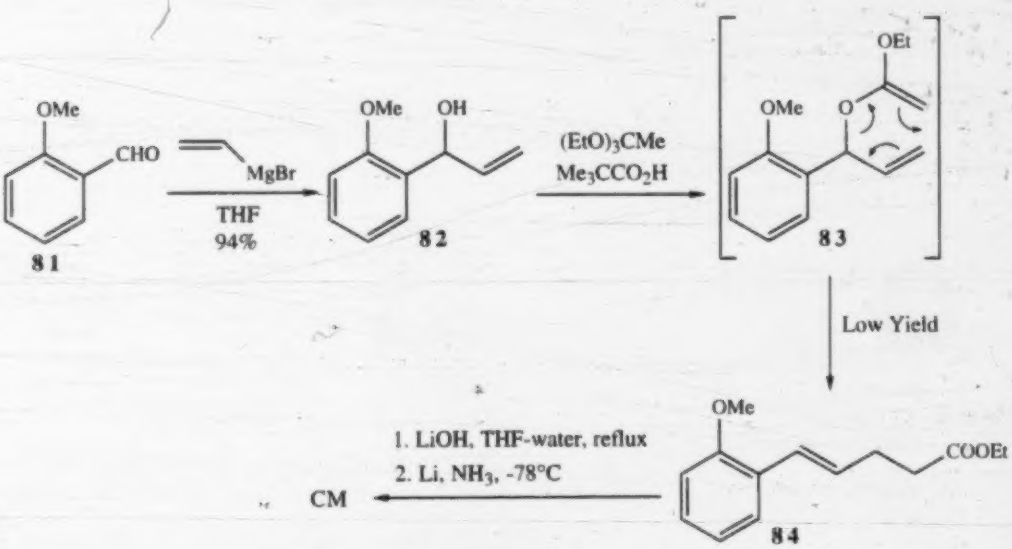


O
OSiMe2t-Bu
5
79
Br2, Et3N
CH2Cl2
Br
80
Jones, KF
acetone, 0°C, 53%
over 2 steps.
4
COOH
64

Scheme 23

Although the above sequence proved to be satisfactory for small scale preparations of bromo acid **64**, it was not suitable for large scale synthesis of this compound; we observed that under those conditions, yields decreased substantially and that purification of the products, although manageable on a milligram scale, was very difficult at the multigram level.

In search for a more practical route, we used the process depicted in Scheme 24. Alcohol **82**, obtained from the reaction between vinylmagnesium bromide and commercially available 2-methoxybenzaldehyde (**81**),[@70] was treated with triethyl orthoacetate in hot (140 °C) pivalic acid.


OMe
CHO
81
MgBr
THF
94%
OMe
OH
82
(EtO)3CMe
Me3CCO2H
OEt
OMe
O
83
Low Yield
OMe
COOEt
84
1. LiOH, THF-water, reflux
2. Li, NH3, -78°C
CM

Scheme 24

The presumed intermediate **83**, which was not isolated, was expected to undergo orthoester-Claisen rearrangement *in situ*. The desired ester **84**,[@70] however, was obtained in very poor yield. A small amount was hydrolyzed to the corresponding carboxylic acid and submitted to the crucial Birch reduction step. We had hoped to effect reduction of the benzene ring and of the side chain double bond, but in the event obtained only a complex mixture.

The difficulties encountered so far prompted us to seek other ways to assemble the basic carbon skeleton of CP-225,917.

2. Radical Cyclization - Second generation.

The disconnection shown in Figure 4 summarizes another attempt to gain entry to the carbobicyclic core of CP-225,917 *via* radical cyclization. In the present case, our intent was to determine if bicyclic structures such as **86** could be made by the 7-*endo*-trig process shown in Scheme 25.

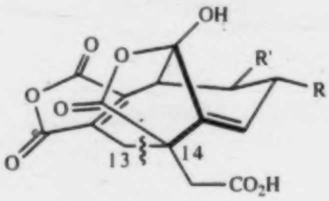
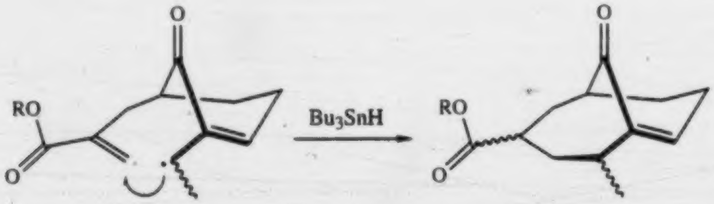


Figure 4 *The second approach to the carbobicyclic substructure of CP-225,917: disconnection between C(13) and C(14).*

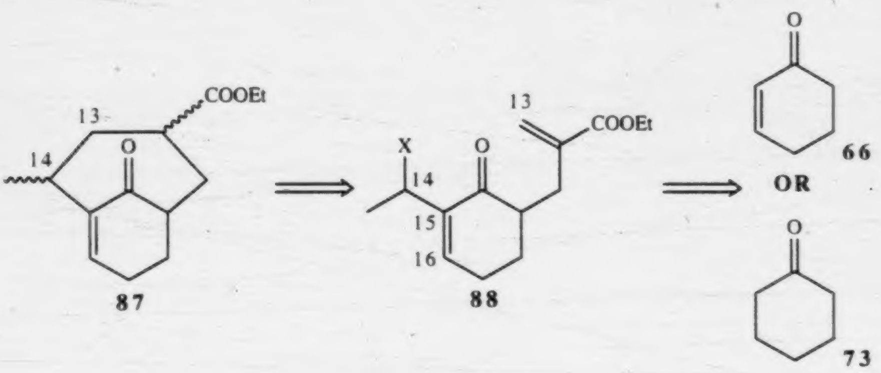


85

86

Scheme 25

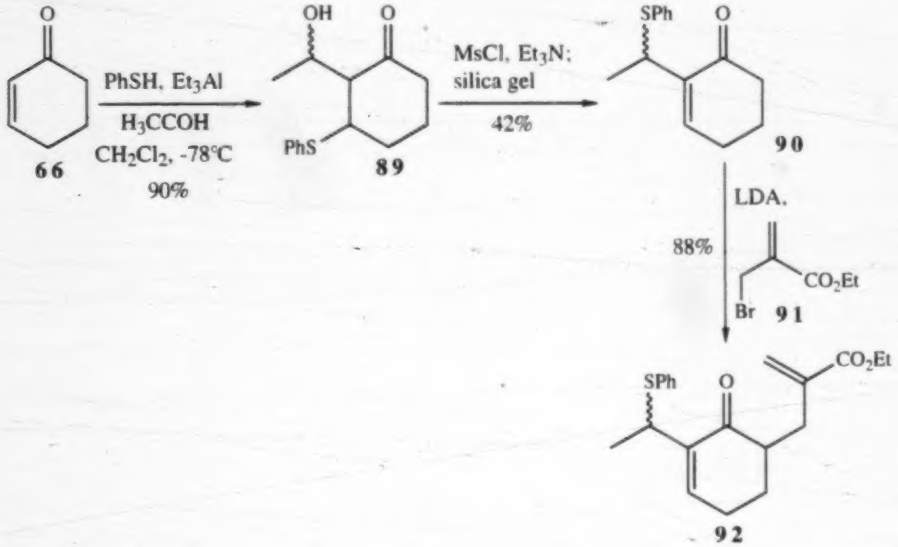
The main target of this strategy was the bridgehead olefin **87** (Scheme 26). Disconnection between C(13) and C(14) leads to the disubstituted cyclohexenone **88**, where



Scheme 26

X is any group capable of undergoing homolytic cleavage. The allylic radical generated in such a process should then attack the conjugated ester (*cf.* Scheme 25, **85→86**). Analysis of simple molecular models suggested that the 7-*endo* process should be favored over the 6-*exo* for steric reasons, but we were unable to predict the behavior of the delocalized radical at C(14)-C(16). Cyclohexenone **88** would be assembled from commercially available materials.

To this end, the aluminum enolate resulting from 1,4-addition of Me_2AlSPh (generated *in situ* from Me_3Al and thiophenol) to 2-cyclohexen-1-one (**66**) was generated, and then subjected to aldol condensation with acetaldehyde[71] to afford alcohol **89** (Scheme 27). Dehydration and rearrangement,[72] then gave enone **90**.

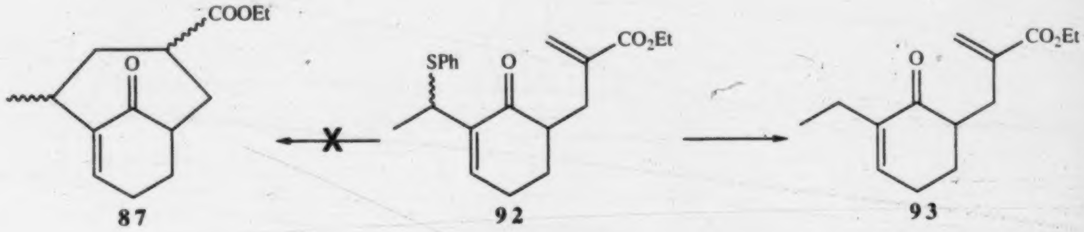

O
66
PhSH, Et_3Al
H_3CCOH
CH_2Cl_2, -78°C
90%
OH
O
PhS
89
MsCl, Et_3N;
silica gel
42%
SPh
O
90
LDA,
88%
CO_2Et
Br
91
CO_2Et
SPh
O
92

Scheme 27

Alkylation of **90** with allylic bromide **91**[73] proceeded well and gave the desired compound **92** in good yield (88%).

The proposed ring closure was attempted by several methods ordinarily employed in radical cyclizations: slow addition of Bu_3SnH and AIBN to a solution of **92** in refluxing PhMe;[74] refluxing of a PhMe solution of Bu_3SnH, AIBN and **92**;[75] and treatment of **92** with Bu_3SnH and Et_3B, in the presence of air, in either PhH or PhMe, at various temperatures.[76]

In no case was the cyclized compound **87** detected, and in some cases, the desulfurized material **93** was the major product (Scheme 28).



Scheme 28

An alternative way of still using compound **92** as the precursor to bicyclic ketone **87** involved $NaIO_4$ oxidation of the thioether moiety to a sulfone, followed by treatment with base. We presumed that a carbanion generated α to the sulfone would undergo 1,4-addition to the unsaturated ester. However, experiments along these lines were not successful.

3. Radical Cyclization - Third generation.

We next studied the synthetic possibilities of a route based on the disconnection shown in Figure 5.

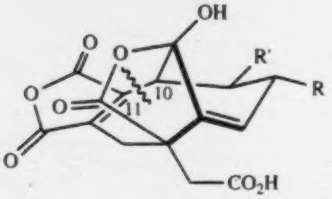
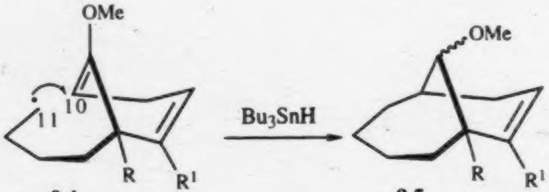


Figure 5 *The third approach to the carbobicyclic substructure of CP-225,917: disconnection between C(10) and C(11).*

This approach is based on an analogous example reported by Beckwith,[77] and requires the chemical bond between C(10) and C(11) to be formed by 7-*endo* radical closure (Scheme 29).

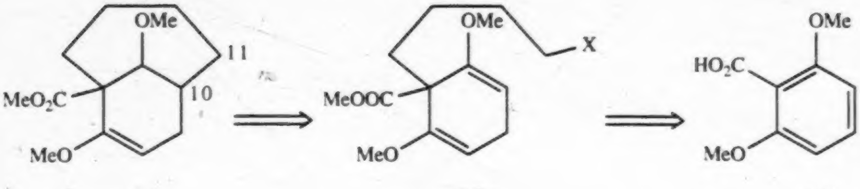


94 **95**

Scheme 29

In this particular case, the bridgehead olefin is not initially installed, and would eventually be constructed by chemical transformation of functional groups R and R^1.

To this end, we chose bicyclic compound **96** as our target (Scheme 30).

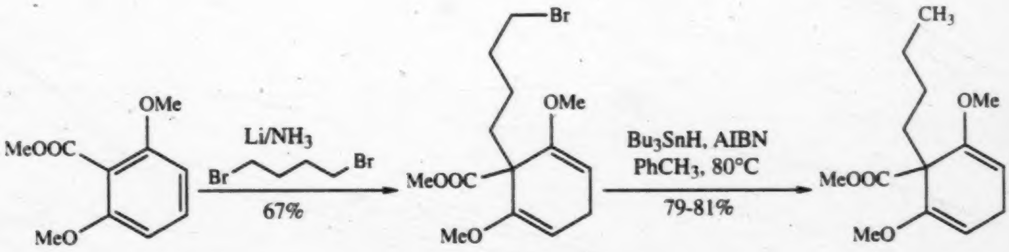

OMe
11
10
MeO2C
MeO
OMe
X
MeOOC
MeO
OMe
HO2C
MeO

96 **97** **98**

Scheme 30

The disconnection presented above leads to diene **97**, where X is a group capable of easily undergoing homolytic cleavage. A reasonable precursor to compounds such as **97** would be 2,6-dimethoxybenzoic acid (**98**).

The synthetic plan was carried out as follows. Esterification of carboxylic acid **98** (MeOH, H_2SO_4, 98%) gave the methyl ester **99**, and Birch reduction (Scheme 31), followed by alkylation with 1,4-dibromobutane, afforded bromide **100** in modest yield. Bromide **100** was then subjected to standard radical cyclization conditions.[74] In our hands,


OMe
MeOOC
MeO
Li/NH3
Br
Br
67%
Br
OMe
MeOOC
MeO
Bu3SnH, AIBN
PhCH3, 80°C
79-81%
CH3
OMe
MeOOC
MeO

99 **100** **101**

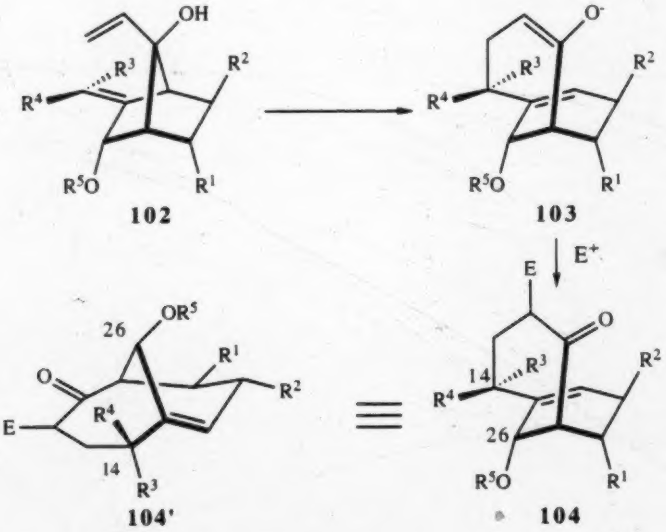
Scheme 31

however, the desired bicyclic product could not be detected; the debrominated compound **101** constituted the major product.

At this point, we decided to look for alternatives to our current approach; our new strategy, which is based on the anionic oxy-Cope rearrangement, will be discussed in the following sections.[78]

4. Anionic oxy-Cope Rearrangement.

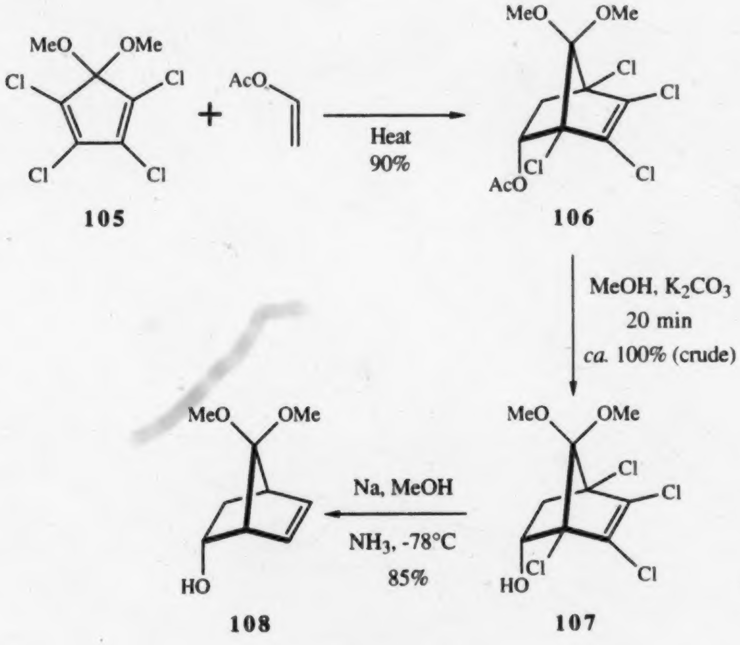
This approach is based on the idea that anionic oxy-Cope rearrangement of compounds such as **102** (Scheme 32) should lead to enolates **103**, which are well suited for further elaboration. In particular, the C(26) oxygen function of **104/104'** could generate the corresponding acetal unit of CP-225,917, and enolates **103** would provide opportunities for constructing the anhydride by initial capture with an electrophile, such as Mander's reagent.[79] The route summarized in Scheme 32, should also be able to accommodate


OH
R3
R2
R4
R5O
R1
102
O-
R3
R2
R4
R5O
R1
103
E+
E
O
14
R3
R2
R4
26
R5O
R1
104
26
OR5
R1
O
R2
E
R4
14
R3
104'

Scheme 32

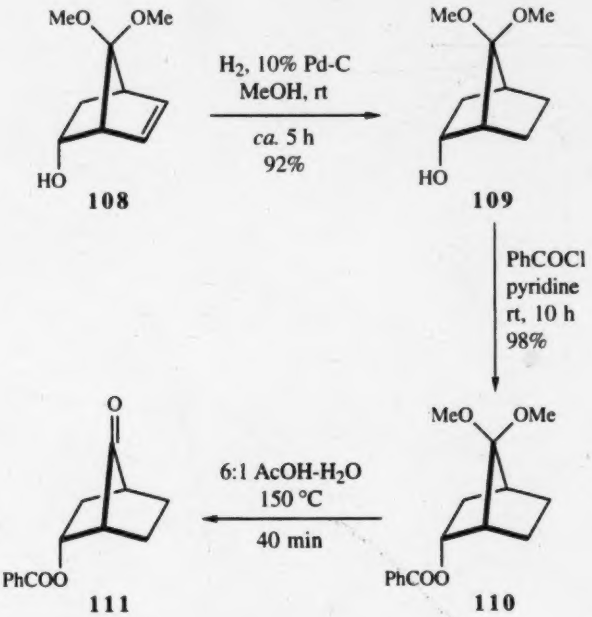
introduction of substituents at C(14), which is a quaternary center in the natural product.

Work on this route began with the straightforward preparation of norbornene **106**, as outlined below (Scheme 33).[80] Diels-Alder condensation of dimethoxytetrachlorocyclopentadiene **105** with vinyl acetate (reflux) affords tetrachloronorbornene **106**, which was easily converted into alcohol **107** by hydrolysis of the acetate. Reductive dechlorination of **107** gave acetal **108**.[81]


MeO
OMe
Cl
AcO
+
Heat
90%
105
106
MeOH, K$_2$CO$_3$
20 min
ca. 100% (crude)
Na, MeOH
NH$_3$, -78°C
85%
HO
108
107

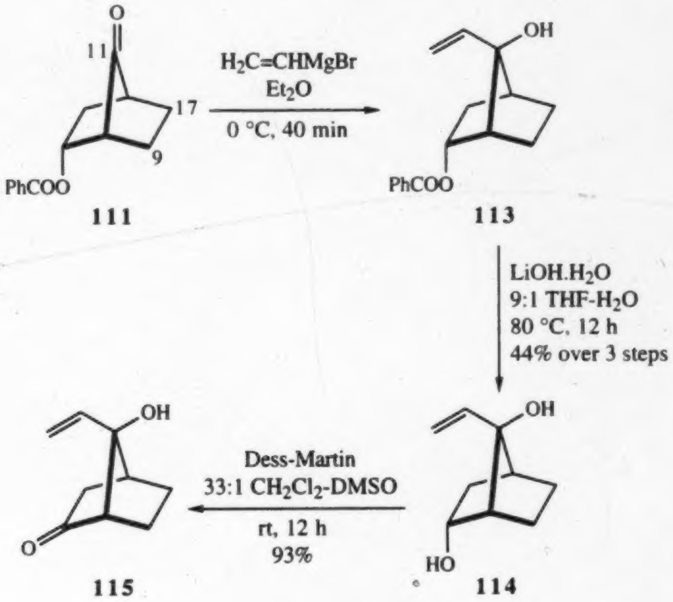
Scheme 33

The double bond of acetal **108** was then saturated, and the resulting alcohol **109**[82] was benzoylated and treated with aqueous acetic acid to hydrolyze the acetal, yielding norbonen-7-one **111** (Scheme 34). Extensive decomposition occurred during attempts at deacetalization of **109** (when esterification was omitted), presumably by a retroaldol process.[83] Ketone **111** is quite sensitive, and so it was used without purification.


MeO
OMe
HO
108
H₂, 10% Pd-C
MeOH, rt
ca. 5 h
92%
109
PhCOCl
pyridine
rt, 10 h
98%
O
PhCOO
111
6:1 AcOH-H₂O
150 °C
40 min
110

Scheme 34

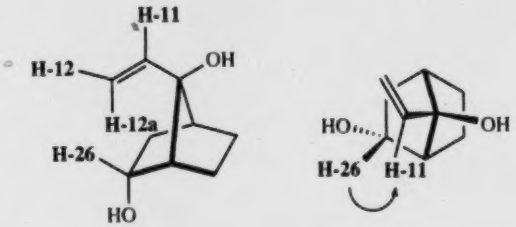
Although introduction of a vinyl group at C(11) by a simple intermolecular process (*cf*. **111**, Scheme 35) could pose serious problems of facial selectivity,[84] we wondered if an adequate level of stereocontrol could be achieved by treatment of crude **111** with vinylmagnesium bromide in Et_2O. Indeed, the reaction gave a ≥5:1 mixture of tertiary


O
11
17
9
PhCOO
111
$H_2C=CHMgBr$
Et_2O
0 °C, 40 min
OH
PhCOO
113
$LiOH.H_2O$
9:1 THF-H_2O
80 °C, 12 h
44% over 3 steps
OH
HO
114
Dess-Martin
33:1 CH_2Cl_2-DMSO
rt, 12 h
93%
OH
O
115

Scheme 35

alcohols, with the desired isomer **113** being the major product, based on the calculated ratio of isolated diol **114** and its C(11) epimer. Separation of the C(11) isomers could be done chromatographically only *after* hydrolysis of the benzoyl group.

The geometry of **114** is supported by NOE enhancement observed for vinyl hydrogen H-11 (DMSO-d_6, δ 6.10) by irradiation of H-26 (DMSO-d_6, δ 4.10) (Figure 6).[85]

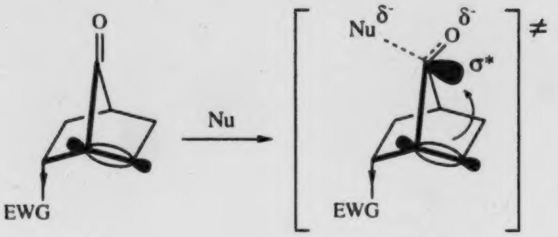


114

Figure 6 *NOE enhancement of H-11 is observed by irradiation of H-26 of compound* ***114***.

The stereochemical outcome of this nucleophilic addition to rigid, sterically unbiased *endo*-substituted-7-norbornanone **111** can be understood on the grounds of two different models: one based on the Cieplak hyperconjugative effect,[86] and the other, on electrostatic effects.[87]

In the first model, the direction of attack follows a simple rule: the nucleophile approaches the carbonyl anti to the best electron-donor bond, presumably because delocalization of the σ electrons of that bond into the incipient σ^* orbital lowers the transition-state energy (*cf.* **111a**, Scheme 36).[84a]

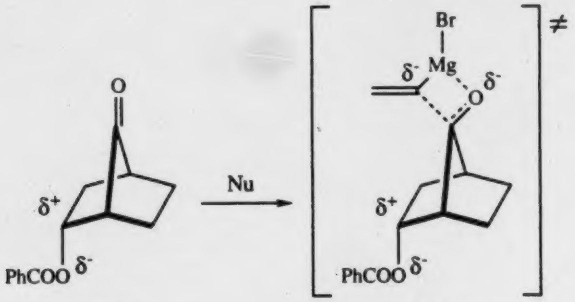

O
EWG
Nu
Nu δ^-
O δ^-
σ*
≠
EWG

111 **111a**

EWG = PhCOO

Scheme 36

The second model, based in great part on *ab initio* molecular orbital calculations,[88] and still under experimental investigation,[89] predicts that the most favorable transition-state will have the partially negatively-charged nucleophile nearer the partially positively-charged carbon atom (*cf.* **111b**, Scheme 37).

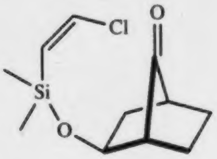

O
δ+
PhCOO δ-
Nu
Br
Mg
δ-
O δ-
δ+
PhCOO δ-
≠

111 **111b**

Scheme 37

Independently of how accurate either model may be,[90] both seem to accommodate our experimental observations.

In a more advanced model, where carbons C(9) and C(17) (*cf.* Scheme 35) of **111** will carry alkyl groups,[91] we expect that steric factors will improve the already satisfactory product ratio.[92] We had actually planned to control the stereochemistry of vinyl addition by using an intramolecular Barbier reaction. Such a procedure would have required preparation of compounds of type **116**. Although

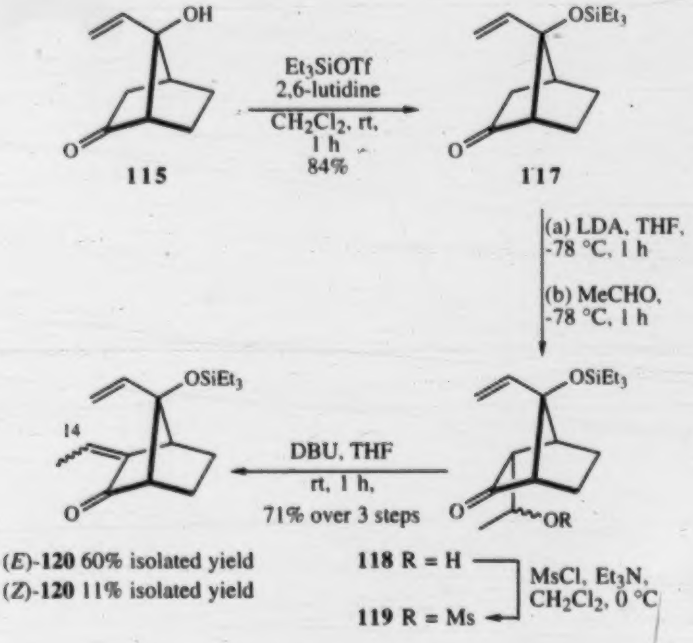


116

synthesis of the required silane ($ClSiMe_2CH=CHCl$) has been reported,[93] the above result suggests that this more involved approach may not be needed.

Oxidation of the major diol (*cf.* **114**, Scheme 35) with the Dess-Martin reagent[94] proceeded smoothly, giving keto alcohol **115** in 93% yield. Other oxidizing agents did not give satisfactory results.

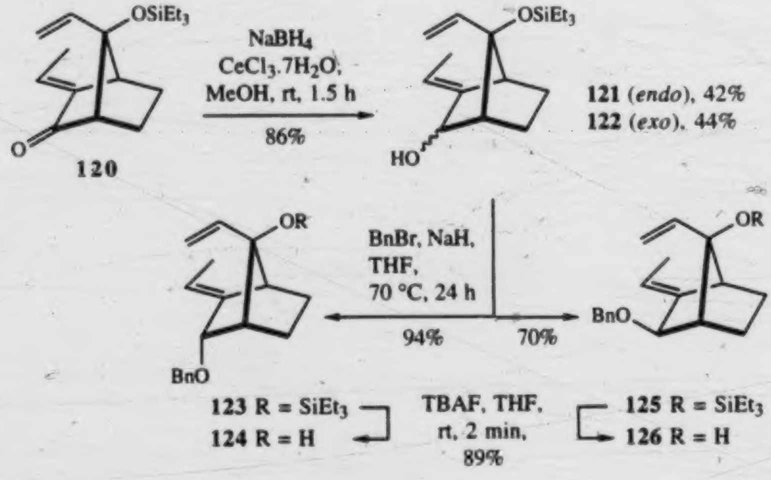
Next, in order to avoid retroaldol fragmentation,[95] the tertiary hydroxyl had to be protected (Scheme 38). Et_3SiOTf in the presence of 2,6-lutidine proved to be a satisfactory


OH
O
115
Et3SiOTf
2,6-lutidine
CH2Cl2, rt,
1 h
84%
OSiEt3
O
117
(a) LDA, THF,
-78 °C, 1 h
(b) MeCHO,
-78 °C, 1 h
OSiEt3
O
OR
118 R = H
119 R = Ms
MsCl, Et3N,
CH2Cl2, 0 °C
DBU, THF
rt, 1 h,
71% over 3 steps
OSiEt3
14
O
(E)-120 60% isolated yield
(Z)-120 11% isolated yield

Scheme 38

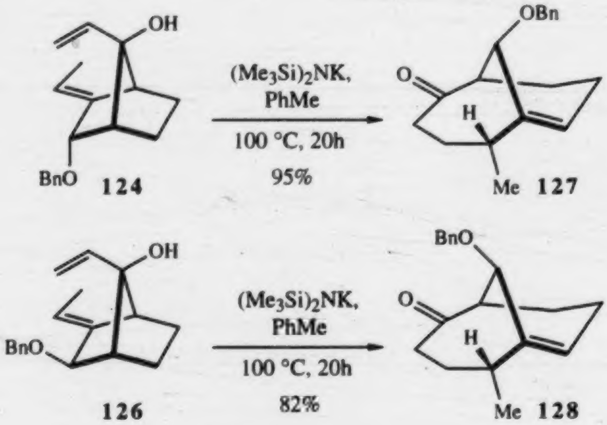
combination of reagents, and gave silyl ether **117** in 84% yield. Several attempts to introduce a *t*-butyldimethylsilyl group were made, no reaction was observed, and only starting material was recovered. We were also unable to find conditions for *p*-methoxybenzylation of alcohol **115** that did not cause extensive decomposition. The remainder of the 1,5-hexadiene subunit required for the anionic oxy-Cope rearrangement was then assembled by a short sequence, beginning with aldol condensation of ketone **117** with MeCHO, so as to form the β-hydroxy ketones **118** as an isomer mixture. Without separation, these alcohols were converted into the corresponding mesylates **119** and, again without isomer separation, the mesylates were treated with DBU, affording the desired enones (*E*)-**120** and (*Z*)-**120**, which were easily separable (*E*-isomer, 60% overall from **117**; *Z*-isomer, 11% overall from **117**). The possibility of conjugate addition for introducing what will eventually be the second substituent at the quaternary center [C(14)] was not explored in this study and, as a matter of convenience, only the major ketone [(*E*)-**120**] was taken further.

Ketone (*E*)-**120** (Scheme 39) was reduced with NaBH$_4$ in the presence of CeCl$_3$·7H$_2$O, affording a 1:1 mixture of *endo*- (**121**; 42% isolated yield) and *exo*-alcohols (**122**; 44%), which were easily separated and individually protected by benzylation (**121→123**, 94%; **122→125**, 70%). Desilylation of both **123** and **125** was accomplished under standard conditions (TBAF, THF) and gave the corresponding alcohols in 89% yield in both cases.


OSiEt$_3$
O
120
NaBH$_4$
CeCl$_3$.7H$_2$O,
MeOH, rt, 1.5 h
86%
OSiEt$_3$
HO
121 (*endo*), 42%
122 (*exo*), 44%
OR
BnO
BnBr, NaH,
THF,
70 °C, 24 h
94%
70%
OR
BnO
123 R = SiEt$_3$
124 R = H
TBAF, THF,
rt, 2 min,
89%
125 R = SiEt$_3$
126 R = H

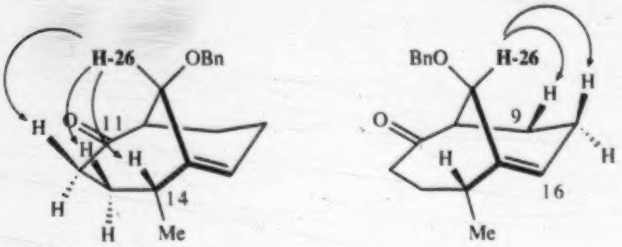
Scheme 39

Each of the resulting alcohols was separately subjected to anionic oxy-Cope conditions and smoothly rearranged, affording respectively, the desired bridgehead keto olefin **127** (95%) and **128** (82%) (Scheme 40).


OH
BnO
124
(Me$_3$Si)$_2$NK,
PhMe
100 °C, 20h
95%
OBn
O
H
Me
127
OH
BnO
126
(Me$_3$Si)$_2$NK,
PhMe
100 °C, 20h
82%
BnO
O
H
Me
128

Scheme 40

Full characterization^{96} by IR, ^{1}H, ^{13}C, COSY, T-ROESY NMR, and MS defines the assigned structures. In particular, T-ROESY measurements show (Figure 7), for compound **127**, strong through-space interaction (NOE) between H-26 (CD_2Cl_2, δ 4.58) and protons located on the C(11)-C(14) arm of the cyclononene system. Conversely, for compound **128**, the same kind of measurements show that H-26 (CD_2Cl_2, δ 5.56) correlates with protons located on the C(9)-C(16) arm of the cyclononene.



127 **128**

Figure 7 *T-ROESY correlation between H-26 and hydrogens located at different sides of the cyclononene substructure of* ***127*** *and* ***128****.*

The structure of the rearrangement products also provides chemical evidence for the geometry assigned to diol **114**.

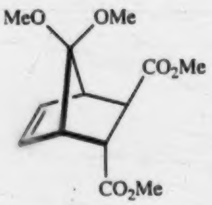
We have not extensively studied ways to increase the rate of the anionic oxy-Cope rearrangement, but a few experiments have shown that the presence of 18-crown-6 does not produce any noticeable enhancement, and the isolated yields of compounds **127** and **128** prepared under these conditions were generally lower.

The above synthesis of bridgehead olefinic ketones **127** and **128**, which represent the [4.3.1]-bicyclic substructure of CP-225,917, offers a promising strategy towards the total synthesis of the natural product, as well as to the closely related CP-263,114 and, of course, to analogues.[97] In the following section, I will briefly describe our exploratory work directed to a more advanced model.

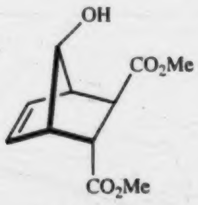
5. Studies Towards an Advanced Model.

The successful use of the anionic oxy-Cope rearrangement described in the previous section provided us with a base from which to proceed with the task of synthesizing an advanced model that would bear features more closely resembling those of the natural product itself.

Close inspection of the type of compounds which generate the required [4.3.1]-bicyclic substructure (*cf.* compounds **102**, Scheme 32) by anionic oxy-Cope rearrangement, indicates that either norbornenes **129**[84a,91d] or **130**,[91a,91b] which are both known compounds, are suitable starting materials for their construction. Notice that alcohol **130** can also, in principle, be converted into acetal **129** by oxidation and acetalization.

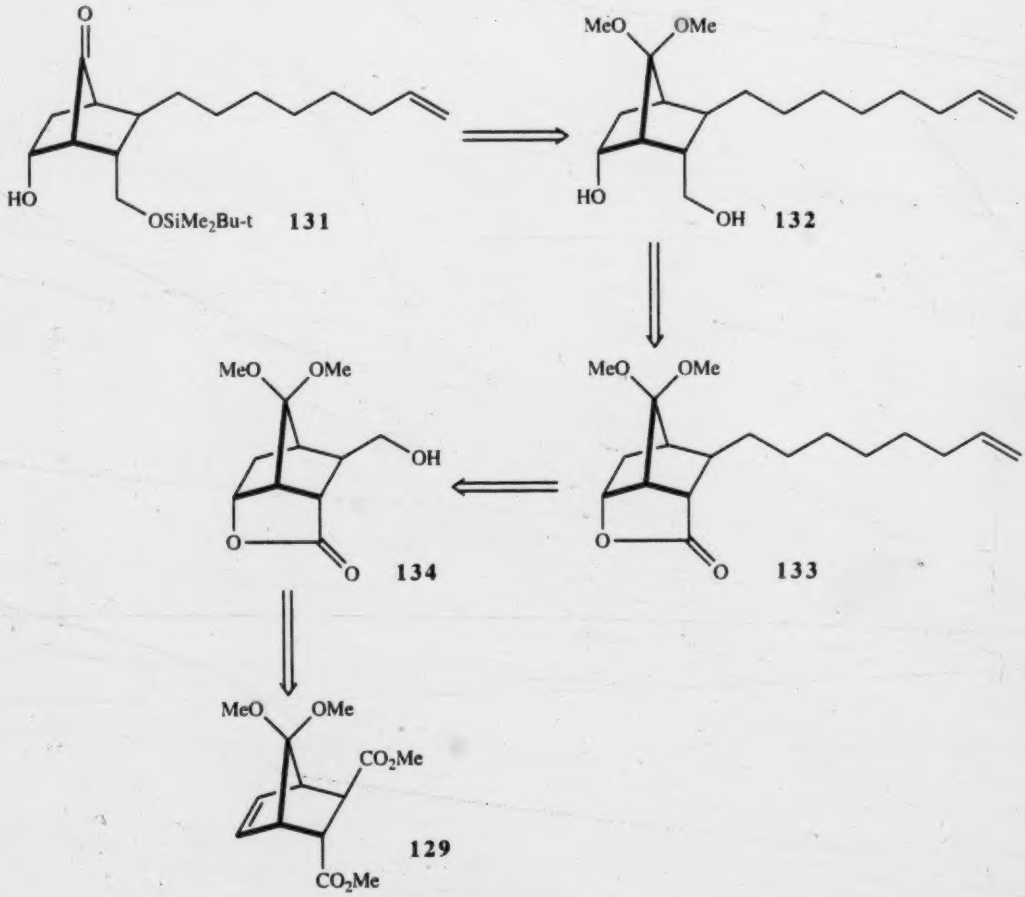


129



130

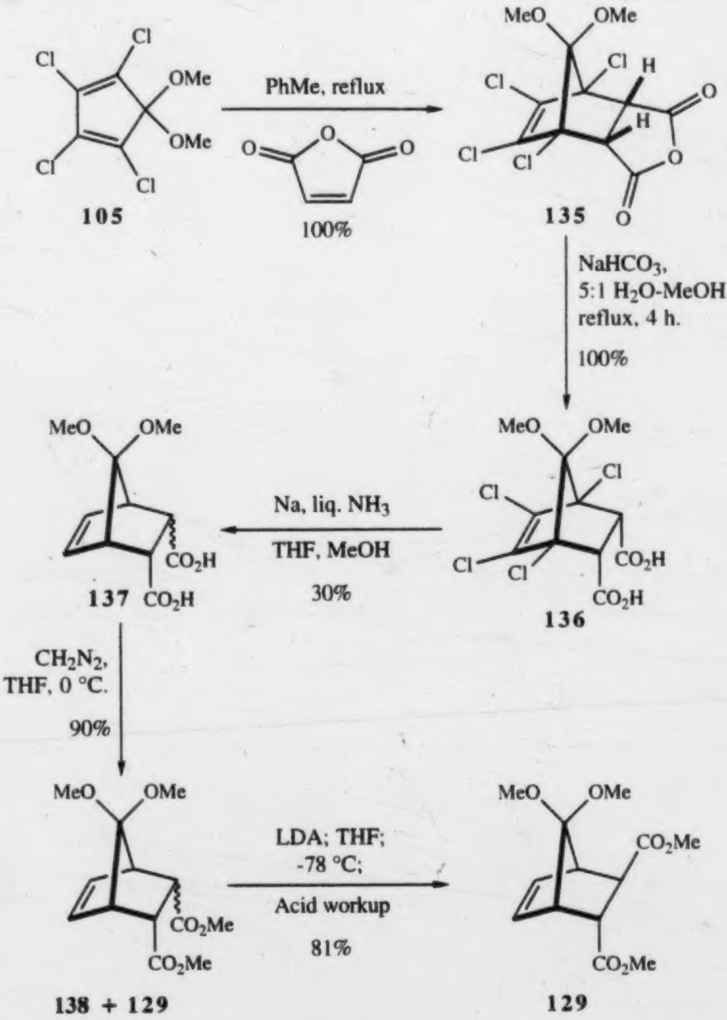
The following retrosynthetic analysis (Scheme 41) illustrates our approach to advanced intermediate **131**, which is an analog of ketone **111** (*cf.* Scheme 35) and would, therefore, probably be amenable to transformations related to those described in the previous section.


O
HO
OSiMe$_2$Bu-t
131
MeO
OMe
HO
OH
132
MeO
OMe
OH
O
O
134
MeO
OMe
O
O
133
MeO
OMe
CO$_2$Me
CO$_2$Me
129

Scheme 41

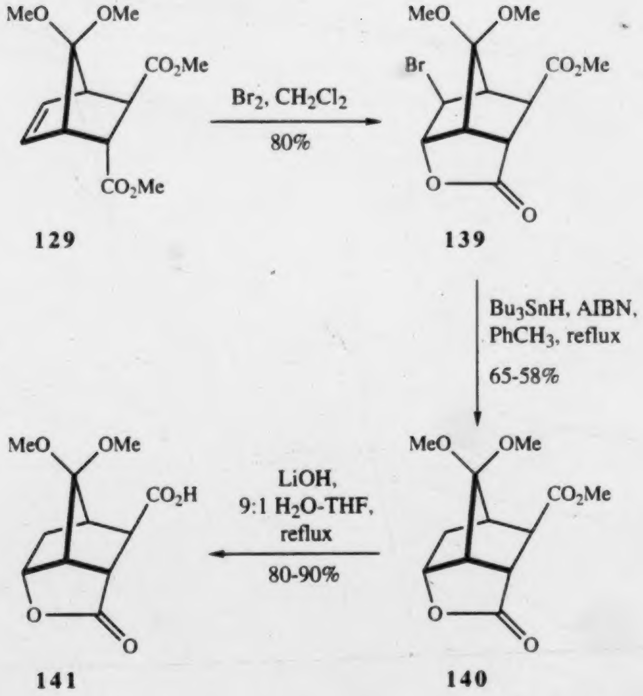
As shown in Scheme 41, ketone **131** could probably be obtained by selective silylation of the primary hydroxyl and deacetalization of diol **132**. We presume that we could gain entry to the 1,4-diol moiety by reduction of lactone **133**. For introduction of the aliphatic chain that is the substituent at C(17) of the natural product, we envision the use of alcohol **134** in which the OH group would be replaced by iodine, followed by coupling with the appropriate organocuprate. The chain at C(9) would be introduced at a later stage. Alcohol **134** should be easy to obtain from acetal **129** by halolactonization, stannane-mediated dehalogenation, and selective reduction of the carboxylic acid derived from the *exo* methyl ester. I will describe my efforts to implement the above plans.

Diester **129** was prepared according to a literature procedure as follows (Scheme 42).[84a,91d] Diels-Alder reaction of tetrachloro diene **105** with maleic anhydride afforded, in excellent yield, the adduct **135** (Scheme 42) which was hydrolyzed to the tetrachloro dicarboxylic acid **136**. Reductive dechlorination of **136** gave dicarboxylic acid **137** in low yield[98] and, on treatment with ethereal diazomethane, this gave a mixture of *anti* (**138**) and *syn* (**129**) dimethyl esters. Treatment of this mixture with LDA followed by acid workup gave only the desired *anti* diester **129**.


PhMe, reflux
100%
NaHCO$_3$,
5:1 H$_2$O-MeOH,
reflux, 4 h.
100%
Na, liq. NH$_3$
THF, MeOH
30%
CH$_2$N$_2$,
THF, 0 °C.
90%
LDA; THF;
-78 °C;
Acid workup
81%
105
135
136
137
138 + 129
129

Scheme 42

Our initial step was bromolactonization of diester **129** (Scheme 43) to afford bromolactone **139**. Radical debromination of **139** gave lactone ester **140**, which was

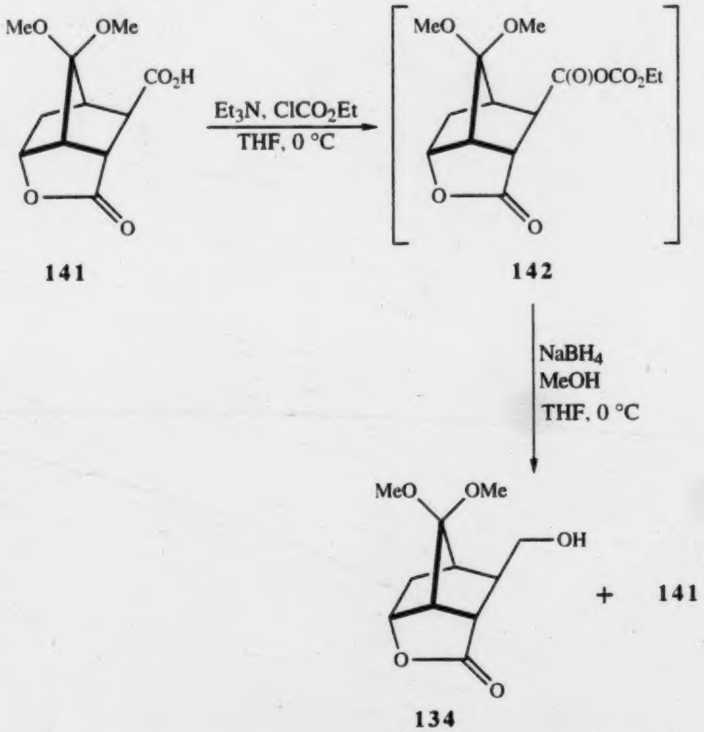

MeO
OMe
CO$_2$Me
CO$_2$Me
129
Br$_2$, CH$_2$Cl$_2$
80%
MeO
OMe
Br
CO$_2$Me
O
O
139
Bu$_3$SnH, AIBN,
PhCH$_3$, reflux
65-58%
MeO
OMe
CO$_2$Me
O
O
140
LiOH,
9:1 H$_2$O-THF,
reflux
80-90%
MeO
OMe
CO$_2$H
O
O
141

Scheme 43

easily converted into lactone acid **141** by hydrolysis of the methyl ester. On treatment with an excess of LiOH in refluxing H_2O-THF, lactone acid **141** did not yield the corresponding dicarboxylic acid, and only starting material (**141**) was isolated; this is probably due to fast relactonization of the 1,4-hydroxy acid that is formed after acid work-up.

Only a few methods to convert carboxylic acid **141** into alcohol **134** have been explored so far, and these preliminary results will be discussed briefly.

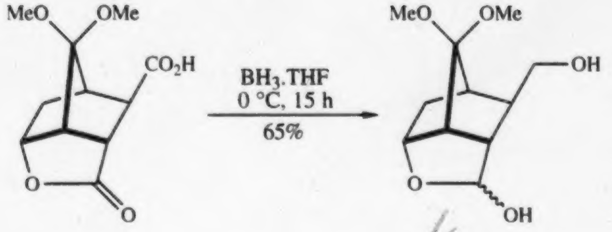
For selective reduction of the carboxyl (Scheme 44), mixed anhydride formation (by reaction with ethyl chloroformate), followed by treatment with NaBH$_4$, gave a


MeO
OMe
CO$_2$H
O
O
141
Et$_3$N, ClCO$_2$Et
THF, 0 °C
MeO
OMe
C(O)OCO$_2$Et
O
O
142
NaBH$_4$
MeOH
THF, 0 °C
MeO
OMe
OH
O
O
134
+ 141

Scheme 44

nearly 1:1 (by NMR) mixture of desired alcohol **134** and parent acid **141** (yield not determined). Mixtures of acids and alcohols can be expected from the reduction of mixed anhydrides such as **142**. We have not optimized this process.

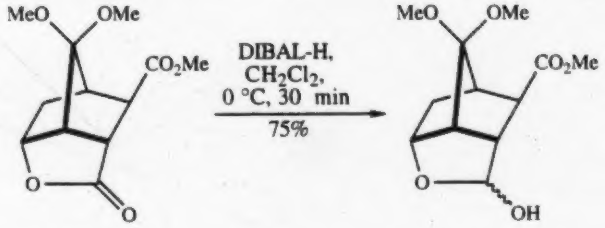
Carboxylic acid **141** was also treated with BH$_3$·THF, and was reduced to lactol-alcohol **143** (Scheme 45).


MeO
OMe
CO2H
BH3.THF
0 °C, 15 h
65%
MeO
OMe
OH
O
O
O
OH

141 **143**

Scheme 45

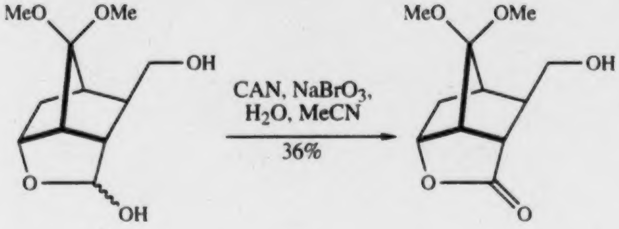
Since carboxylic acids are generally more sensitive to those conditions than esters and lactones, we expected some degree of selectivity towards reduction of the carboxyl. On the other hand, the lactone moiety of lactone-ester **140** was selectively reduced on treatment with DIBAL-H (Scheme 46).[99]


MeO
OMe
CO2Me
DIBAL-H,
CH2Cl2,
0 °C, 30 min
75%
MeO
OMe
CO2Me
O
O
O
OH

140 **144**

Scheme 46

Selective oxidation of the lactol moiety of **143** in the presence of the primary alcohol, could also provide an entry to lactone alcohol **134**. Thus, treatment of **143** with a catalytic amount of CAN in the presence of $NaBrO_3$[100] afforded



143 **134**

Scheme 47

lactone-alcohol **134** (Scheme 47), but in low yield. This procedure has not been optimized. Further work aimed at generating **134** in an efficient manner is currently under way.

Conclusions.

Synthesis of bridgehead olefinic ketones **127** and **128** by anionic oxy-Cope rearrangement of 3-hydroxyl-1,5-dienes **124** and **126**, represents a promising strategy towards the total synthesis of both natural products CP-225,917 and the closely related CP-263,114. Several intermediates obtained in this work can be further elaborated, allowing us to explore other aspects of our approach.

A few experiments directed to the construction of more advanced models have also been undertaken. Alcohol **134** was prepared by two related methods and experimental work along the lines described in Scheme 41 will be carried out in this laboratory.

III. Experimental Section

General Procedures. Unless stated to the contrary, the following conditions apply: Reactions were carried out under a slight static pressure of Ar that had been purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[101] and then through a similar column of Drierite. All solvents for reactions were dried as described below. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of Ar. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Hexane used for chromatography was distilled before use.

Products were isolated from solution by evaporation under water aspirator vacuum at room temperature, using a rotary evaporator.

Microliter syringes were washed with water and acetone, using a suction device to draw the solvents through. Then air was sucked through for 1 min. The solution to be dispensed was drawn up and expelled, and this operation was repeated several times before drawing up the sample to be used. Cannula transfers were always done under slight pressure (Ar), not by suction.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F-254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid[102] or 2,4-dinitrophenylhydrazine in 2N HCl,[103] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by dry syringes fitted with oven-dried needles, or by cannula. Dry tetrahydrofuran (THF) and Et_2O were distilled from sodium benzophenone ketyl. Dry PhMe was distilled from sodium. Dry Et_3N, *i*-Pr_2NH, CH_2Cl_2, and pyridine were distilled from CaH_2. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

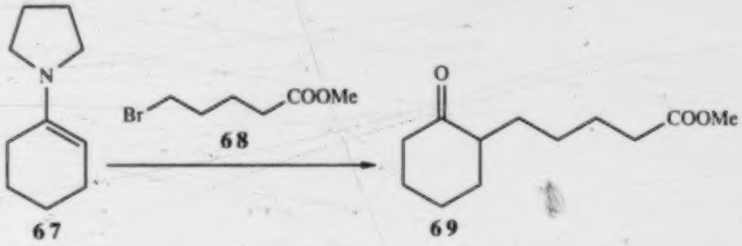
FT-IR measurements were recorded on a Nicolet 7000 FTIR instrument. Measurements were made as casts from the specified solvent using potassium bromide plates.

^1H nuclear magnetic resonance spectra were recorded with Bruker AM-300 (at 300 MHz), Varian INOVA-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent. ^{13}C spectra were recorded with Bruker AM-300 (at 75.5 MHz) or Varian UNITY-500 (at 125 MHz). The symbols s', d', t', and q' used for ^{13}C NMR signals indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with AEI Models MS-12 or MS-50 mass spectrometers at an ionizing voltage of 70eV.

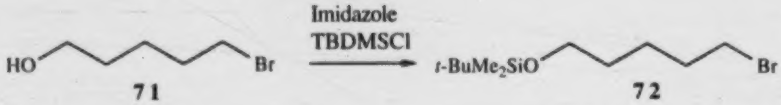
Compounds isolated by flash chromatography were homogeneous by TLC and, unless otherwise stated, were pure as judged by high field ^1H NMR spectra.

Methyl 5-(2-Oxocyclohexyl)pentanoate (69).



A solution of enamine **67** (0.82 mL, 5.1 mmol) and bromoester **68** (995.0 mg, 5.101 mmol) in PhMe (5 mL) was refluxed for 15 h. The mixture was quenched with water (2 mL), and stirring under reflux was continued for 2 h. The aqueous phase was extracted with Et_2O (2 mL). The combined organic phases were washed with 5% aqueous hydrochloric acid (2 x 10 mL), saturated aqueous $NaHCO_3$ (10 mL) and brine (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 15 cm), using 1:4 EtOAc-hexane, gave compound **69** (217.0 mg, 22% yield) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 1659, 1590, 992 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.05-1.35 (m, 4 H), 1.45-1.65 (m, 4 H), 1.65-1.82 (m, 2 H), 1.89-2.06 (m, 2 H), 2.10-2.30 (m, 5 H), 3.60 (s, 3 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.79, 24.90, 26.57, 27.90, 28.90, 33.78, 41.88, 50.36, 51.27, 173.95, 212.94 (two signals overlap); exact mass *m/z* calcd for $C_{12}H_{20}O_3$ 212.1412, found 212.1408. Anal. Calcd for $C_{12}H_{20}O_3$: C 67.88 , H 9.50. Found: C 67.90, H 9.50.

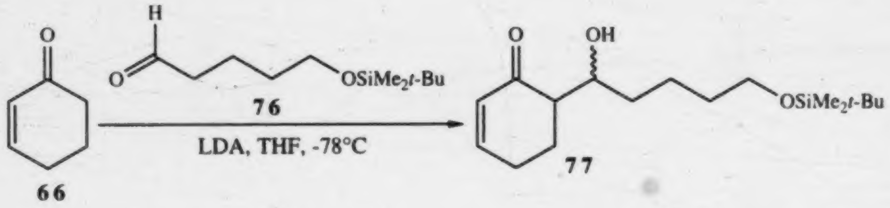
(5-Brompentyloxy)(1,1-dimethylethyl)dimethylsilane (72).



71 **72**

t-BuMe$_2$SiCl (5.44 g, 36.1 mmol) and imidazole (5.10 g, 74.9 mmol) were added to a stirred solution of 5-bromopentan-1-ol (**71**) (5.00 g, 29.9 mmol) in CH$_2$Cl$_2$ (20 mL). Stirring was continued for 15 min, and water (5 mL) was then added. The aqueous phase was extracted with CH$_2$Cl$_2$ (5 mL), and the combined organic phases were washed with water (5 mL) and brine (5 mL), dried (MgSO$_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using petroleum ether, gave compound **72** (8.3 g, 99% yield) as a colorless oil: FTIR (CH$_2$Cl$_2$ cast) 2929, 1104, 835 cm^{-1}; ^{1}H NMR (300 MHz, CDCl$_3$) δ 0.05 (s, 6 H), 0.89 (s, 9 H), 1.40-1.60 (m, 4 H), 1.88 (ddd, J = 14.0, 7.0, 7.0 Hz, 2 H), 3.40 (t, J = 7.0 Hz, 2 H), 3.61 (t, J = 6.0 Hz, 2 H); ^{13}C NMR (75.5 MHz, CDCl$_3$) δ -5.26, 18.36, 24.63, 25.69, 31.94, 32.65, 33.80, 62.88; exact mass m/z calcd for C$_7$H$_{16}$^{81}BrOSi (M - C$_4$H$_9$) 225.0133, found 225.0130. Anal. Calcd for C$_{11}$H$_{25}$BrOSi: C 46.97 , H 8.96. Found: C 47.13, H 9.20.

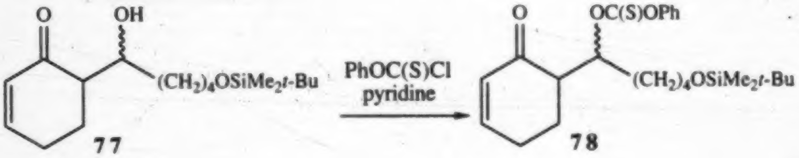
2-[1-Hydroxy-5-[(1,1-dimethylethyl)dimethylsiloxy]pentyl]-cyclohex-5-enone (77).



A solution of 2-cyclohexen-1-one (**66**) (0.19 mL, 2.0 mmol) in THF (1 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (2.2 mmol, 1.1 eq.) in THF (2 mL). The solution was then stirred for 1 h, and a solution of aldehyde **76** (391.5 mg, 1.809 mmol) in THF (1 mL) was added in one portion. After 10 min, the mixture was quenched at -78 °C by addition of saturated aqueous NH_4Cl (2 mL). The cold bath was removed and the mixture was allowed to warm to room temperature, diluted with Et_2O (3 mL), and extracted with water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3.0 x 15 cm), using 1:4 EtOAc-petroleum ether, gave alcohol **77** (338.5 mg, 60% yield) as a colorless oil: FTIR ($CHCl_3$ cast) 3477, 2929, 1665, 1099, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.01 (s, 6 H), 0.80 (s, 9 H), 1.30-1.60 (m, 4 H), 1.68 (dddd, *J* = 13.0, 9.0, 7.0, 7.0 Hz, 2 H), 1.95-2.10 (m, 2 H), 2.30 (ddd, *J* = 12.0, 7.5, 4.5 Hz, 1 H), 2.35-2.41 (m, 2 H), 3.55-3.61 (m, 2 H), 3.78-3.88 (m, 1 H), 4.0 (br s, 1 H), 5.97 (dt, *J* = 10.0, 2.0 Hz, 1 H), 6.96 (dddd, *J*

= 10.0, 5.0, 3.5, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.25, 18.37, 21.16, 25.12, 25.87, 26.00, 32.85, 33.44, 51.55, 63.18, 71.66, 129.91, 150.89, 203.71; exact mass *m/z* calcd for $C_{17}H_{32}O_3Si$ 312.2121, found 312.2119. Anal. Calcd for $C_{17}H_{32}O_3Si$: C 65.33 , H 10.32. Found: C 65.70, H 10.55.

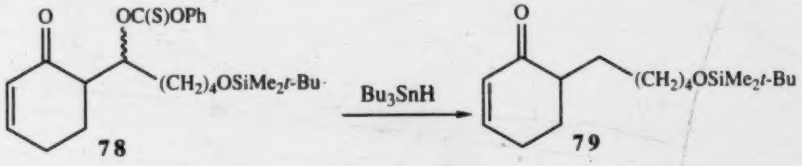
5-[(1,1-Dimethylethyl)dimethylsiloxy]-1-[2-oxocyclohex-3-enyl]pentyl phenyl thiocarbonate (78).



Pyridine (0.11 mL, 1.4 mmol) and PhOC(S)Cl (0.06 mL, 0.4 mmol) were added to a stirred solution of alcohol **77** (107.3 mg, 0.3432 mmol) in CH_2Cl_2 (2.5 mL). Stirring at room temperature was continued for 5 h. The solvent was evaporated, and flash chromatography of the residue over silica gel (2.0 x 15 cm), using 1:9 EtOAc-hexane, gave compound **78** (141.6 mg, 92% yield) as a yellow oil: FTIR (CH_2Cl_2 cast) 2928, 1678, 1198 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.40-1.70 (m, 5 H), 1.75-1.84 (m, 1 H), 1.88-2.02 (m, 1 H), 2.10-2.22 (m, 1 H), 2.41-2.50 (m, 2 H), 3.06 (dt, *J* = 13.0, 4.0 Hz, 1 H), 3.62-3.66 (m, 2 H), 5.98-6.02 (m, 2 H), 6.94-7.01 (m, 1 H), 7.10-7.50 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.26, 22.32, 23.06, 25.62, 26.00, 29.72, 32.46, 48.99, 62.88, 84.23, 121.98, 126.49,

129.46, 130.02, 149.90, 153.34, 194.53, 197.69 (the signal corresponding to the quaternary carbon of the *t*-butyl group could not be detected under the experimental conditions); exact mass *m/z* calcd for $C_{20}H_{27}O_4SSi$ (M - C_4H_9) 391.1399, found 391.1401. Anal. Calcd for $C_{24}H_{36}O_4SSi$: C 64.25 , H 8.09. Found: C 64.87, H 8.23.

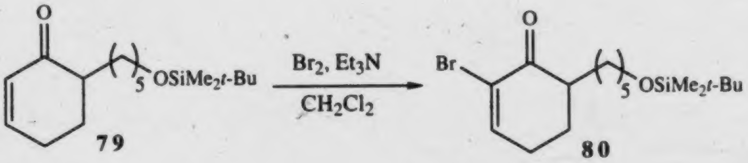
2-[5-[(1,1-Dimethylethyl)dimethylsiloxy]pentyl]cyclohex-5-enone (79).



A solution of Bu_3SnH (0.10 mL, 0.37 mmol) in PhMe (10 mL) and a solution of AIBN (6.1 mg, 0.037 mmol) in PhMe (10 mL) were added dropwise over 12 h (syringe pump) to a stirred and hot (80 °C) solution of compound **78** (112.1 mg, 0.2665 mmol) in PhMe (20 mL). Stirring was continued for 1 h after the end of the addition, and the solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2.0 x 17 cm), using 1:9 EtOAc-hexane, gave deoxygenated compound **79** (66.7 mg, 90% yield) as a colorless oil: FTIR (CH_2Cl_2 cast) 2929, 1680, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 0.05 (s, 6 H), 0.85 (s, 9 H), 1.28-1.42 (m, 5 H), 1.52 (app quintet, *J* = 6.5 Hz, 2 H), 1.69-1.86 (m, 2 H), 2.10 (app dq, *J* = 13.0, 5.0 Hz, 1 H), 2.22-2.30 (m, 1

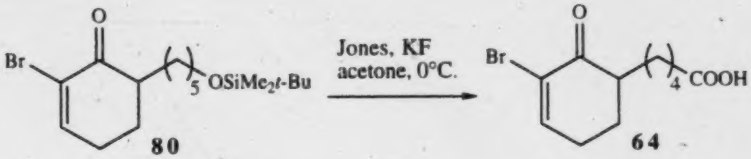
H), 2.32-2.40 (m, 2 H), 3.59 (t, *J* = 6.5 Hz, 2 H), 5.96 (dt, *J* = 10.0, 2.0 Hz, 1 H), 6.90 (app dtd, *J* = 10.5, 4.5, 0.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ -5.25 (q'), 18.38 (s'), 25.03 (t'), 25.95 (t'), 26.00 (q'), 26.83 (t'), 27.73 (t'), 29.14 (t'), 32.77 (t'), 46.58 (d'), 63.20 (t'), 129.58 (d'), 149.30 (d'), 201.99 (s'); exact mass *m/z* calcd for $C_{17}H_{32}O_2Si$ 296.2171, found 296.2172.

2-Bromo-6-[5-[(1,1-dimethylethyl)dimethylsiloxy]pentyl]cyclohex-2-enone (80).



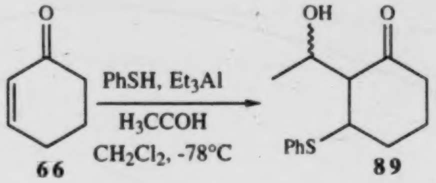
A solution of Br_2 (22.8 μL, 0.443 mmol) in CH_2Cl_2 (0.5 mL) was added dropwise to a stirred and cooled (0 °C) solution of enone **79** (125.4 mg, 0.4229 mmol) in CH_2Cl_2 (1.0 mL). Stirring at 0 °C was continued for 2 h. Neat Et_3N (0.1 mL, 0.7 mmol) was then added dropwise, the cold bath was removed, and stirring was continued for 4 h. The mixture was then quenched with saturated aqueous NH_4Cl (1 mL), and extracted with CH_2Cl_2 (5 mL). The organic phase was washed with water (1 mL) and brine (1 mL), dried ($MgSO_4$) and evaporated. The product was not characterized, and the crude bromoenone **80** (175.4 mg) was used directly in the next step.

5-[3-Bromo-2-oxocyclohex-3-enyl]pentanoic acid (64).



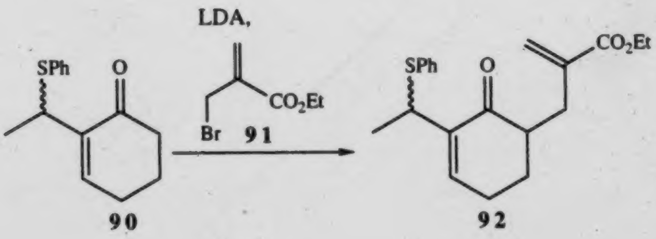
Jones reagent [prepared by dissolving CrO_3 (267.2 mg, 2.672 mmol) in a mixture of H_2SO_4 (0.23 g, *ca.* 2.4 mmol) and water (1 mL)] (0.21 mL) was added dropwise to a stirred and cooled (0 °C) solution of bromoenone **80** (175.4 mg, *ca.* 0.4672 mmol) in acetone (2 mL). Stirring at 0 °C was continued for 1 h, and water (4 mL) was then added. The solution was extracted with CH_2Cl_2 (4 x 4 mL), and the combined organic phases were washed with water (5 mL) and brine (3 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 20 cm), using 1:19 MeOH-$CHCl_3$, gave carboxylic acid **64** (61.8 mg, 53% yield) as a foam: FTIR ($CHCl_3$ cast) 3043, 2936, 1692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30-1.50 (m, 3 H), 1.65 (app quintet, J = 6.5 Hz, 2 H), 1.76-1.95 (m, 2 H), 2.13 (app dq, J = 14.0, 7.5 Hz, 1 H), 2.36 (t, J = 7.0 Hz, 2 H), 2.40-2.50 (m, 3 H), 7.35 (t, J = 4.0 Hz, 1 H), 8.00-11.00 (br s, 1 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 24.58, 26.33, 27.38, 27.65, 29.21, 33.80, 47.15, 123.71, 150.03, 179.65, 193.52; exact mass *m/z* calcd for $C_{11}H_{13}{}^{81}BrO_2$ (M - H_2O) 258.0079, found 258.0074.

2-(1-Hydroxyethyl)-3-(phenylthio)cyclohexanone (89).


O
66
PhSH, Et3Al
H3CCOH
CH2Cl2, -78°C
OH
O
PhS
89

Compound **89** was prepared according to a literature procedure,[71] which did not report analytical data. Compound **89** had: FTIR (CH_2Cl_2 cast) 3441, 2937, 1706 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.32 (d, J = 6.6 Hz, 3 H), 1.58-1.71 (m, 1 H), 1.75-1.88 (m, 1 H), 2.00-2.12 (m, 1 H), 2.18-2.28 (m, 1 H), 2.29-2.36 (m, 3 H), 2.68 (br s, 1 H), 3.52 (td, J = 9.5, 4.0 Hz, 1 H), 4.38 (dq, J = 7.0, 3.0 Hz, 1 H), 7.25-7.45 (m, 5 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 22.49, 24.73, 31.85, 42.35, 50.44, 60.85, 67.15, 128.05, 129.36, 133.49, 133.93, 211.87 (the isolated material appears to be a single diastereoisomer); exact mass *m/z* calcd for $C_{14}H_{18}O_2S$ 250.1027; found 250.1021.

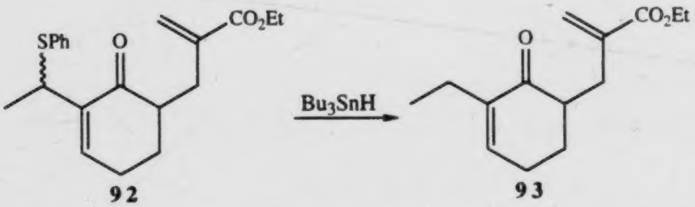
Ethyl 2-[[2-Oxo-3-[1-(phenylthio)ethyl]cyclohex-3-enyl]-methyl]propenoate (92).


SPh
O
90
LDA,
CO2Et
Br
91
SPh
O
CO2Et
92

A solution of ketone **90** (70.9 mg. 0.305 mmol) in THF (1 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (0.328 mmol, 1.08 eq.) in THF (2 mL). The mixture was then stirred for 1 h, and neat allylic bromide **91** (66.3 mg, 0.319 mmol) was added in one portion. After 1 h, the mixture was quenched at -78 °C by addition of saturated aqueous NH_4Cl (1 mL). The cold bath was removed and the mixture was allowed to warm to room temperature, and diluted with Et_2O (4 mL). The organic layer was washed with water (2 mL) and brine (2 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:5.66 EtOAc-hexane, gave compound **92** (92.5 mg, 88% yield) as a yellow oil which was an inseparable mixture of diastereoisomers: FTIR (CH_2Cl_2 cast) 2925, 1714, 1673 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 1.30 (two overlapping triplets, *J* = 7.0 Hz, 6 H), 1.35 (dd, *J* = 7.0, 1.5 Hz, 6 H), 1.50-1.65 (m, 2 H), 2.01 (dq, *J* = 13.0, 3.5 Hz, 2 H), 2.20 (ddd, *J* = 13.5, 8.5, 3.5 Hz, 2 H), 2.29-2.40 (m, 4 H), 2.48-2.60 (m, 2 H), 2.94-3.10 (m, 2 H), 4.20 (two overlapping quartets, *J* = 7.0, 1.2 Hz, 4 H), 4.41-4.51 (m, 2 H), 5.51 (s, 2 H), 6.25 (t, *J* = 1.5 Hz, 2 H), 6.78 (t, *J* = 4.0 Hz, 1 H), 6.82 (t, *J* = 4.0 Hz, 1 H), 7.15-7.35 (m, 10 H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ 14.23, 20.94, 21.01, 25.11, 25.32, 27.38, 27.64, 32.04, 32.19, 39.32, 39.39, 45.81, 60.74, 126.86, 126.96, 127.00, 127.02, 128.70, 132.15, 132.29, 135.04, 135.19, 138.59, 138.68, 140.04, 140.11, 144.50, 144.85, 167.00, 167.04, 198.56, 198.70 (several signals of the two diastereomers coincide);

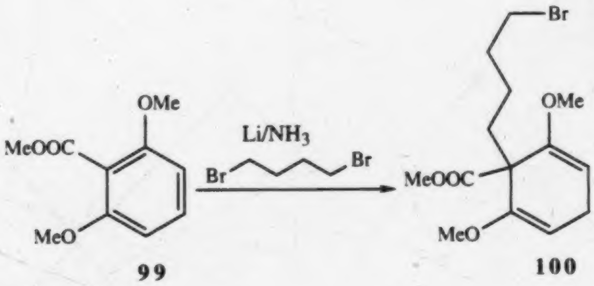
exact mass *m/z* calcd for $C_{20}H_{24}O_3S$ 344.1446, found 344.1448. Anal. Calcd for $C_{20}H_{24}O_3S$: C 69.74 , H 7.02, found: C 69.50, H 6.87.

Ethyl 2-[[3-Ethyl-2-oxocyclohex-3-enyl]methyl]propenoate (93).



A solution of Bu_3SnH (0.08 mL, 0.3 mmol) in PhH (10 mL) and a solution of AIBN (15.0 mg, 0.0913 mmol) in PhH (10 mL) were added dropwise over 10 h (syringe pump) to a stirred solution of compound **92** (90.0 mg, 0.261 mmol) in refluxing PhH (20 mL). The solution was cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (3.0 x 16 cm), using 1:13.3 EtOAc-hexane, gave reduced compound **93** (24.8 mg, 40% yield) as a yellow oil: FTIR (CH_2Cl_2 cast) 2933, 1715, 1671, 1176 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.97 (t, *J* = 7.0 Hz, 3 H), 1.28 (t, *J* = 7.0 Hz, 3 H), 1.51-1.70 (m, 2 H), 2.01 (app qd, *J* = 13.5, 1.0 Hz, 1 H), 2.11-2.21 (m, 2 H), 2.30-2.39 (m, 2 H), 2.49 (app d quintets, *J* = 11.5, 4.5 Hz, 1 H), 3.0 (ddd, *J* = 14.5, 5.0, 1.1 Hz, 1 H), 4.20 (q, *J* = 7.0 Hz, 2 H), 5.55 (dd, *J* = 2.5, 1.5 Hz, 1 H), 6.19 (d, *J* = 1.1 Hz, 1 H), 6.63 (app tq, *J* = 3.5, 1.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 13.10, 14.36, 23.03, 24.64, 28.25, 32.55, 46.12, 61.00, 126.53, 139.52, 140.89, 143.20, 167.23, 200.47; exact mass *m/z* calcd for $C_{14}H_{20}O_3$ 236.1412, found 236.1418.

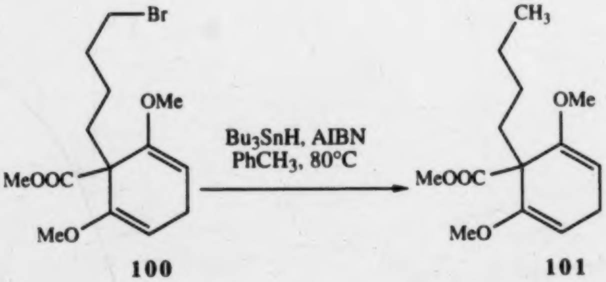
Methyl [1-(5-Bromopentyl)-2,6-dimethoxycyclohexa-2,5-dienyl]-carboxylate (100).



A solution of aromatic ester **99** (1.00 g, 5.10 mmol) and *t*-BuOH (0.50 mL, 5.3 mmol) in THF (6 mL) was added dropwise to a vigorously stirred and cooled (-78 °C) solution of Li (78 mg, 11 mmol) in liquid NH_3 (36 mL). After 1 h, neat 1,4-dibromopropane (1.52 mL, 12.7 mmol) was added in one portion. Stirring was continued for 1 h, and the mixture was then quenched by adding solid NH_4Cl. The ammonia was allowed to evaporate overnight. The residue was partitioned between Et_2O (50 mL) and water (20 mL). The aqueous phase was extracted once with Et_2O, and the combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5.0 x 17 cm), using 1:9 EtOAc-hexane, gave bromide **100** (1.19 g, 67% yield)

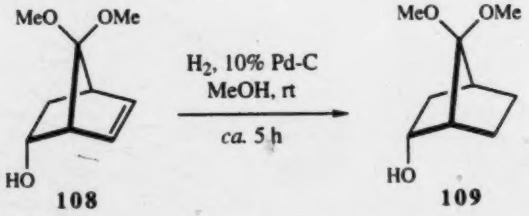
as a colorless oil: FTIR (CH_2Cl_2 cast) 3000, 2948, 1745, 1697, 1243 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.10-1.21 (m, 2 H), 1.81 (app quintet, *J* = 7.5 Hz, 2 H), 1.90-1.96 (m, 2 H), 2.85 (app t, *J* = 3.8 Hz, 2 H), 3.39 (t, *J* = 7.0 Hz, 2 H), 3.50 (s , 6 H), 3.61 (s, 3 H), 4.88 (app t, *J* = 3.8 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 24.38, 25.76, 30.30, 33.16, 34.42, 52.54, 55.06, 93.72, 152.45, 173.15 (the signal corresponding to quaternary carbon at the ring could not be detected under the experiment conditions); exact mass *m/z* calcd for $C_{14}H_{21}{}^{81}BrO_4$ 334.0603, found 334.0596.

Methyl (2,6-Dimethoxy-1-pentylcyclohexa-2,5-dienyl)-carboxylate (101).



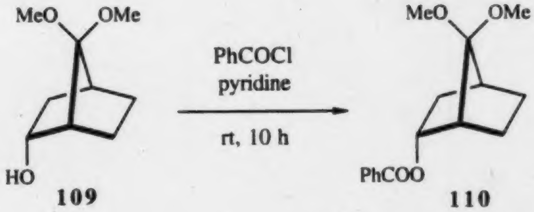
A solution of Bu_3SnH (0.16 mL, 0.60 mmol) in PhH (10 mL) and a solution of AIBN (4.0 mg, 0.024 mmol) in PhH (10 mL) were added dropwise over 18 h (syringe pump) to a stirred solution of bromide **100** (133 mg, 0.400 mmol) in refluxing PhH (30 mL). The solution was cooled to room temperature and evaporated. The residue was diluted with Et_2O (30 mL) and added to 60% aqueous KF (10 mL). The mixture was stirred vigorously for 12 h at room temperature. The organic phase was separated and washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 16 cm), using 1:9 EtOAc-hexane, gave compound **101** (81.9 mg, 81% yield) as a colorless oil: FTIR (CH_2Cl_2 cast) 2952, 1746, 1696, 1207, 1138 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.84 (t, J = 7.1 Hz, 3 H), 0.93-1.04 (m, 2 H), 1.27 (dddd, J = 14.5, 7.1, 7.1, 7.1 Hz, 2 H), 1.85-1.94 (m, 2 H), 2.81-2.86 (m, 2 H), 3.50 (s, 6 H), 3.60 (s, 3 H), 4.86 (t, J = 3.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.27, 23.16, 24.42, 26.36, 31.19, 52.47, 55.03, 93.46, 152.84, 173.38 (the signal corresponding to the quaternary carbon on the ring could not be detected under the experimental conditions); exact mass *m/z* calcd for $C_{14}H_{22}O_4$ 254.1518, found 254.1512.

***Endo*-7,7-Dimethoxybicyclo[2.2.1]heptan-2-ol (109).**



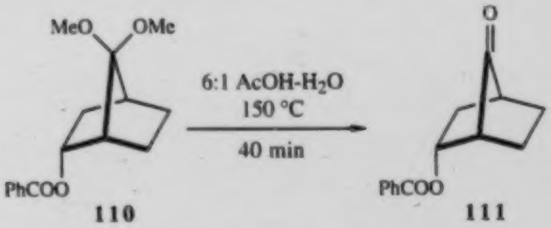
A mixture of unsaturated alcohol **108** (332.8 mg, 1.955 mmol) in MeOH (10 mL) and 10% Pd-C (28.1 mg) was stirred under hydrogen (balloon) at room temperature. When all starting material had been consumed (*ca* 5 h, TLC control, silica, 2:3 EtOAc-hexane) the solvent was evaporated. The resulting black sludge was suspended in Et_2O and filtered through a small pad of flash chromatography silica gel. Evaporation of the filtrate, and flash chromatography of the residue over silica gel (1.5 x 16 cm), using 2:3 EtOAc-hexane, gave saturated alcohol **109** (309.2 mg, 92% yield) as a pale yellow oil: FTIR (CH_2Cl_2 cast) 3406, 2961, 1069 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.94 (dd, *J* = 12.5, 3.5 Hz, 1 H), 1.25-1.35 (m, 1 H), 1.48-1.60 (m, 1 H), 1.72-1.92 (m, 2 H), 2.01 (app t, *J* = 9.0, 4.5 Hz, 1 H), 2.13 (dd, *J* = 5.0, 4.0 Hz, 1 H), 2.18 (dddd, *J* = 12.5, 9.5, 5.0, 3.0 Hz, 1 H), 3.20 (s, 3 H), 3.22 (s, 3 H), 4.36 (dddd, *J* = 8.0, 6.0, 5.0, 1.5 Hz, 1 H) (the hydrogen at the hydroxyl could not be discerned); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 17.97 (t'), 27.95 (t'), 38.85 (t'), 39.00 (d'), 44.26 (d'), 50.13 (q'), 50.61 (q'), 70.54 (d'), 114.47 (s'); exact mass *m/z* calcd for $C_9H_{16}O_3$ 172.1099, found 172.1098.

endo-7,7-Dimethoxybicylo[2.2.1]heptan-2-yl Benzoate (110).



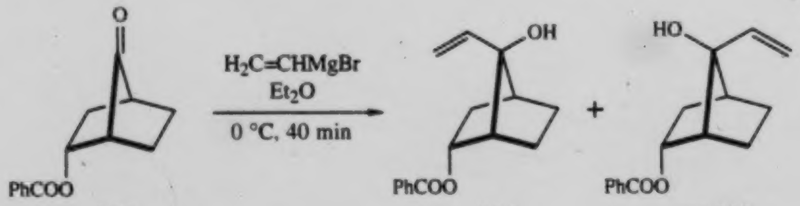
PhCOCl (0.08 mL, 0.7 mmol) was added in one portion to a stirred solution of alcohol **109** (102.3 mg, 0.5902 mmol) in dry pyridine (1.0 mL), and the solution was stirred for 10 h. The solvent was evaporated and the residue taken up in Et_2O, washed with water, saturated aqueous $NaHCO_3$, and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 15 cm), using 1:20 EtOAc-hexane, gave benzoate **110** (160.1 mg, 98%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2957, 1789, 1717, 1213 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.28 (dd, J = 3.0, 13.0 Hz, 1 H), 1.36-1.47 (m, 1 H), 1.60-1.72 (m, 1 H), 1.82-1.95 (m, 2 H), 2.13 (app t, J = 4.5 Hz, 1 H), 2.38 (dddd, J = 12.8, 9.6, 4.5, 2.7 Hz, 1 H), 2.50 (app t, J = 4.5 Hz, 1 H), 3.25 (s, 3 H), 3.27 (s, 3 H), 5.27-5.35 (m, 1 H), 7.42-7.49 (m, 2 H), 7.54-7.61 (m, 1 H), 8.01-8.06 (m, 2 H); ^{13}C NMR (75.5 MHz, CH_2Cl_2) δ 19.11 (t'), 27.73 (t'), 36.22 (t'), 38.58 (d'), 42.50 (d'), 50.33 (q'), 50.82 (q'), 74.64 (d'), 114.07 (s'), 128.73 (d'), 129.76 (d'), 131.13 (s'), 133.17 (d'), 166.49 (s'); exact mass *m/z* calcd for $C_{16}H_{20}O_4$ 276.1362, found 276.1365.

endo-7-Oxobicylo[2.2.1]heptan-2-yl Benzoate (111).



A solution of benzoate **110** (65.5 mg, 0.237 mmol) in 6:1 (v/v) AcOH-H_2O (3.5 mL) was heated at 150 °C for 40 min, cooled to room temperature and evaporated. The residue was diluted with Et_2O and washed successively with saturated aqueous $NaHCO_3$, water and brine, dried ($MgSO_4$) and evaporated. The product could not be chromatographed (decomposition), and so the crude ketone **111** (54.3 mg) was used directly in the next step. The crude material had: FTIR (CH_2Cl_2 cast) 2949, 1778, 1719, 1111 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.67-1.84 (m, 3 H), 1.94-2.05 (m, 1 H), 2.09 (app t, J = 4.5 Hz, 1 H), 2.13-2.24 (m, 1 H), 2.45 (app t, J = 4.5 Hz, 2 H), 2.52 (dddd, J = 15.0, 7.5, 4.5, 3.0 Hz, 1 H), 5.41 (dddd, J = 7.9, 5.8, 4.8, 2.0 Hz, 1 H), 7.44-7.52 (m, 2 H), 7.58-7.64 (m, 1 H), 8.02-8.12 (m, 2 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 15.89 (t'), 24.06 (t'), 34.90 (t'), 40.59 (d'), 44.38 (d'), 69.02 (d'), 128.85 (d'), 129.84 (d'), 130.47 (s'), 133.54 (d'), 166.24 (s'), 212.27 (s'); exact mass m/z calcd for $C_{14}H_{14}O_3$ 230.0943, found 230.0941.

(2*R,7*S**)- and (2*R**,7*R**)-7-Ethenyl-7-hydroxybicylo[2.2.1]heptan-2-yl Benzoate (113 and *epi*-113).**

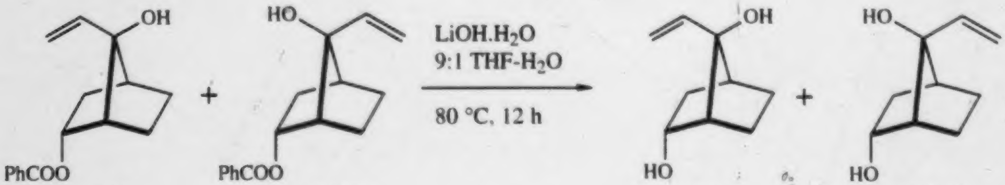


111 **113** ***epi*-113**

Vinylmagnesium bromide (1 M, 1.14 mL, 1.14 mmol) was added dropwise to a stirred and cooled (0 °C) solution of crude ketone **111** (239.4 mg, ≤1.040 mmol) in Et_2O (10 mL).

The reaction was monitored by TLC (silica, 1:4 EtOAc-hexane) and, after 40 min, no more starting material could be detected. The mixture was quenched with saturated aqueous NH_4Cl and the organic phase was washed once with water. The combined aqueous phases were extracted twice with Et_2O. The combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.5 x 25 cm), using 1:4 EtOAc-hexane, gave pure alcohol **113** (20.9 mg) along with a mixture of alcohols **113** and *epi*-**113** (168.9 mg). The geometry of **113** was assigned by NOE measurements. Isomer **113** had: FTIR (CH_2Cl_2 cast) 3459, 2959, 1716, 1278 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.34 (dd, *J* = 12.9, 2.8 Hz, 1 H), 1.46 (ddd, *J* = 12.3, 10.1, 4.5 Hz, 1 H), 1.52-1.68 (m, 1 H), 1.80 (dddd, *J* = 15.7, 9.0, 4.5, 4.5 Hz, 1 H), 1.97 (ddd, *J* = 13.4, 9.5, 4.0 Hz, 2 H), 2.33 (app t, *J* = 3.9 Hz, 1 H), 2.66 (dddd, *J* = 12.9, 10.1, 5.0, 3.4 Hz, 1 H), 5.26 (dd, *J* = 10.0, 1.3 Hz, 1 H), 5.44 (dd, *J* = 17.4, 1.3 Hz, 1 H), 5.56-5.64 (m, 1 H), 6.29 (dd, *J* = 17.4, 10.0 Hz, 1 H), 7.46 (app t, *J* = 7.91 Hz, 2 H), 7.58 (dt, *J* = 7.9, 1.7 Hz, 1 H), 8.01-8.07 (m, 2 H) (the hydrogen at the hydroxyl could not be discerned); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 19.20 (t'), 27.67 (t'), 36.85 (t'), 44.43 (d'), 47.98 (d'), 76.39 (d'), 86.85 (s'), 115.83 (t'), 128.70 (d'), 129.74 (d'), 131.18 (s'), 133.12 (d'), 139.19 (d'), 166.63 (s'); exact mass *m/z* calcd for $C_{16}H_{18}O_3$ 258.1256, found 258.1254.

(2*R**,7*S**)- and (2*R**,7*R**)-7-Ethenylbicylo[2.2.1]heptan-2,7-diol (114 and *epi*-114).



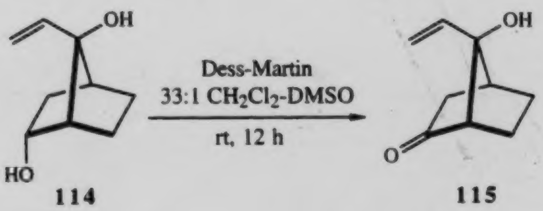
113 *epi*-**113** **114** *epi*-**114**

A mixture of diastereomers **113** and *epi*-**113** (1.40 g, 5.42 mmol) and LiOH·H_2O (455 mg, 10.8 mmol) in 9:1 (v/v) THF-H_2O (20 mL) was refluxed (oil bath, 80 °C) for 12 h, cooled to room temperature, diluted with Et_2O (20 mL), and washed with water (5 mL). The aqueous phase was extracted with Et_2O (2 x 5 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (16 x 4.0 cm), using 1:1 EtOAc-hexane, gave diol **114** (435.5 mg, 44% yield from **110**) and diol *epi*-**114** (80.0 mg, 9% yield from **110**) as crystalline solids. The major isomer (**114**; geometry determined by NOE) had: mp 117-127 °C; FTIR 3262, 2950, 1001 cm^{-1}; ^1H NMR (DMSO-d_6 and CD_2Cl_2) δ 0.88 (dd, *J* = 12.0, 4.0 Hz, 1 H), 1.18-1.28 (m, 1 H), 1.68 (td, *J* = 5.2, 1.3 Hz, 1 H), 1.74 (app t, *J* = 3.9 Hz, 1 H), 1.84 (app t, *J* = 3.9 Hz, 1 H), 1.88-2.09 (m, 3 H), 4.09-4.16 (m, 1 H), 4.18 (d, *J* = 4.0 Hz, 1 H), 4.28 (s, 1 H), 5.08 (dd, *J* = 10.0, 2.0 Hz, 1 H), 5.32 (dd, *J* = 18.0, 2.0 Hz, 1 H), 6.13 (dd, *J* = 18.0, 10.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6 and $CDCl_3$) δ 18.38 (t'), 28.50 (t'), 38.03 (t'), 43.92

(d'), 50.43 (d'), 67.94 (d'), 83.59 (s'), 114.18 (t'), 139.65 (d'); exact mass *m/z* calcd for $C_9H_{14}O_2$ 154.0994, found 154.0987.

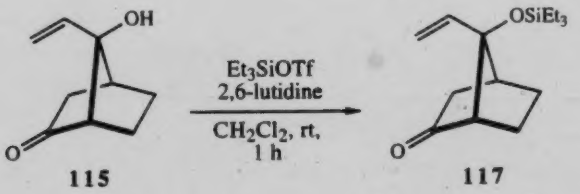
The minor isomer (*epi*-**114**; geometry determined by NOE) had: mp 105-110 °C; FTIR (CH_2Cl_2 cast) 3346, 2954, 1038 cm^{-1}; ^1H NMR (DMSO-d_6) δ 0.83 (dd, *J* = 12.0, 3.0 Hz, 1 H), 1.16-1.38 (m, 2 H), 1.53-1.68 (m, 2 H), 1.70 (app t, *J* = 4.5 Hz, 1 H), 1.90 (ddd, *J* = 12.0, 9.0, 5.0 Hz, 1 H), 2.20-2.31 (m, 1 H), 4.37 (d, *J* = 4.0 Hz, 1 H), 4.41-4.49 (m, 1 H), 4.67 (s, 1 H), 5.06 (dd, *J* = 11.0, 2.3 Hz, 1 H), 5.29 (dd, *J* = 17.3, 2.3 Hz, 1 H), 6.15 (dd, *J* = 17.3, 11.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, DMSO-d_6) δ 17.54 (t'), 27.30 (t'), 44.11 (d'), 49.03 (d'), 69.97 (d'), 85.25 (s'), 113.87 (t'), 140.27 (d') [one signal overlaps with one of the solvent signals, but can be observed at δ 39.59 (t') in a (poor quality) spectrum run in CD_2Cl_2]; exact mass *m/z* calcd for $C_9H_{12}O$ (M - H_2O) 136.0888, found 136.0886.

anti-7-Ethenyl-7-hydroxybicyclo[2.2.1]heptan-2-one (115).



A mixture of diol **114** (100 mg, 0.649 mmol) and Dess-Martin periodinane (382 mg, 0.900 mmol) was stirred in 33.3:1 CH_2Cl_2-DMSO (10.3 mL). After 12 h, the white suspension was diluted with Et_2O (10 mL) and washed successively with saturated aqueous $NaHCO_3$ (containing 10% $Na_2S_2O_5$), and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica-gel (1.5 x 15 cm), using 1:2.5 EtOAc-hexane, gave **115** as a colorless oil (327.2 mg, 93%): FTIR (CH_2Cl_2 cast) 3416, 2957, 1739, 1079 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.48 (d, *J* = 7.0 Hz, 2 H), 1.89 (d, *J* = 17.5 Hz, 2 H), 2.19-2.26 (m, 3 H), 2.30-2.34 (m, 1 H), 2.44-2.48 (m, 1 H), 5.24 (dd, *J* = 11.0, 1.0 Hz, 1 H), 5.34 (dd, *J* = 17.5, 1.0 Hz, 1 H), 6.11 (dd, *J* = 17.5, 11.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 22.75 (t'), 27.06 (t'), 43.80 (d'), 45.23 (t'), 57.67 (d'), 84.00 (s'), 117.69 (t'), 138.32 (d'), 215.13 (s'); exact mass *m/z* calcd for $C_9H_{12}O_2$ 152.0837, found 152.0837.

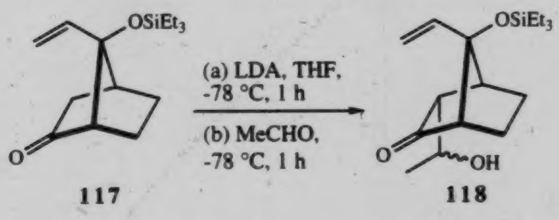
anti-7-Ethenyl-7-[(triethylsilyl)oxy]bicyclo[2.2.1]heptan-2-one (117).



Et_3SiOTf (0.10 mL, 0.44 mmol) was added dropwise to a stirred and cooled (0 °C) solution of **115** (98.7 mg, 0.320

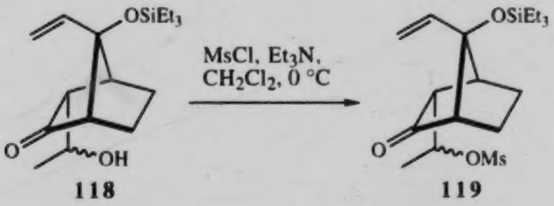
mmol) and 2,6-lutidine (0.05 mL, 0.4 mmol) in CH_2Cl_2 (2.5 mL). After 1 h, the mixture was quenched with saturated aqueous $NaHCO_3$ (1 mL), diluted with Et_2O (5 mL), and washed successively with 10% aqueous hydrochloric acid, saturated aqueous $NaHCO_3$, water, and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:20 EtOAc-hexane, gave **117** (72.0 mg, *ca.* 84%), containing slight impurities (^{1}H NMR): FTIR (CH_2Cl_2 cast) 2955, 1753 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.60 (q, *J* = 7.5 Hz, 6 H), 0.90 (t, *J* = 7.5 Hz, 9 H), 1.44 (dd, *J* = 11.0, 1.5 Hz, 2 H), 1.81 (d, *J* = 18.0 Hz, 1 H), 2.13-2.25 (m, 3 H), 2.27-2.31 (m, 1 H), 2.51 (d, *J* = 3.5 Hz, 1 H), 5.23 (dd, *J* = 11, 0.9 Hz, 1 H), 5.24 (dd, *J* = 18.0, 0.9 Hz, 1 H), 6.09 (dd, *J* = 18.0, 11.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.65 (t'), 7.06 (q'), 23.07 (t'), 27.11 (t'), 44.53 (d'), 44.59 (t'), 57.14 (d'), 85.90 (s'), 118.55 (t'), 138.40 (d'), 215.41 (s'); exact mass *m/z* calcd for $C_{14}H_{26}O_2Si$ 266.1702, found 266.1700.

(3*S,7*S**)-7-Ethenyl-3-(1-hydroxyethyl)-7-[(triethylsilyl)-oxy]bicylo[2.2.1]heptan-2-one (118).**



A solution of ketone **117** (64.0 mg, 0.240 mmol) in THF (1 mL) was added dropwise to a stirred and cooled (-78 °C) solution of LDA (0.264 mmol, 1.10 eq.) in THF (1.5 mL). The solution was then stirred for 1 h, and neat MeCHO (20.0 μL, 0.358 mmol) was added in one portion. After 1 h, the mixture was quenched at -78 °C by addition of saturated aqueous NH_4Cl (1 mL). The cold bath was removed and the mixture was allowed to warm to room temperature, diluted with Et_2O, and just enough water to dissolve the precipitated salts was then added. The organic phase was washed successively with water and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 17 cm), using 1:10 EtOAc-hexane, gave alcohol **118** as a mixture of diastereomers (56.4 mg, 76%). The material was a colorless oil: FTIR (CH_2Cl_2 cast) 3516, 2957, 1732, 1116 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.60 (q, *J* = 7.5 Hz, 6 H), 0.93 (t, *J* = 7.5 Hz, 9 H), 1.09 (d, *J* = 6.0 Hz, 3 H), 1.40-1.60 (m, 1 H), 1.87 (d, *J* = 9.8 Hz, 2 H), 2.09-2.21 (m, 1 H), 2.21-2.40 (m, 2 H), 2.65 (dd, *J* = 5.0, 1.2 Hz, 1 H), 3.65 (s, 1 H), 3.91 (dd, *J* = 12.5, 11.9 Hz, 1 H), 5.31 (dd, *J* = 10.5, 0.9 Hz, 1 H), 5.33 (dd, *J* = 17.5, 0.9 Hz, 1 H), 6.09 (dd, *J* = 17.5, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.62 (t'), 7.02 (q'), 21.63 (q'), 22.27 (t'), 29.24 (t'), 47.73 (d'), 56.52 (d'), 62.50 (d'), 69.25 (d'), 85.19 (s'), 119.97 (t'), 139.27 (d'), 219.87 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_3Si$ 310.1964, found 310.1959.

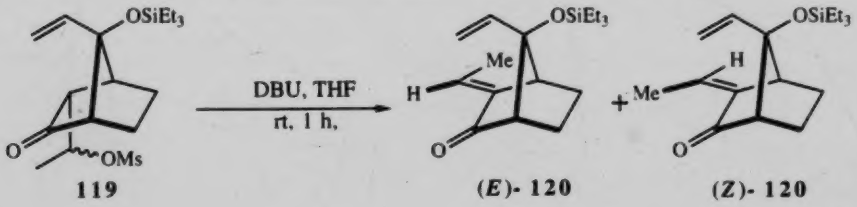
(3*S,7*S**)-7-Ethenyl-3-(1-hydroxyethyl)-7-[(triethylsilyl)-oxy]bicylo[2.2.1]heptan-2-one Methanesulfonate (119).**



$MeSO_2Cl$ (51.0 µL, 0.654 mmol) was added dropwise to a stirred and cooled (0 °C) solution of alcohol **118** (mixture of diastereomers, 102 mg, 0.327 mmol) and Et_3N (91.0 µL, 0.654 mmol) in CH_2Cl_2 (4 mL). After 1 h, the mixture was diluted with Et_2O (5 mL) and quenched with saturated aqueous $NaHCO_3$ (1 mL). The organic phase was washed successively with water and brine, dried ($MgSO_4$) and evaporated. The resulting oil (115.0 mg) was used in the next step without further purification. Flash chromatography of a small sample (20.5 mg) over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave mesylate **119** (16.3 mg, 63%), containing traces of the minor stereoisomer (^{1}H NMR; the geometry was not established), as a colorless oil: FTIR (CH_2Cl_2 cast) 2912, 2876, 1749, 1176 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.60 (q, *J* = 7.5 Hz, 6 H), 0.94 (t, *J* = 7.5 Hz, 9 H), 1.40 (d, *J* = 6.1 Hz, 3 H), 1.46-1.66 (m, 2 H), 2.17 (d, *J* = 9.5 Hz, 2 H), 2.26 (dd, *J* = 4.0, 1.5 Hz, 1 H), 2.30-2.42 (m, 1 H), 2.68 (dd, *J* = 4.0, 1.5 Hz, 1 H), 2.97 (s, 3 H), 4.75 (ddq, *J* = 10.0, 10.0, 6.5 Hz, 1 H), 5.37 (dd, *J* = 17.5, 0.9 Hz, 1 H), 5.39 (dd, *J* =

11.0, 0.9 Hz, 1 H), 6.15 (dd, *J* = 17.5, 11.0 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.59, 7.00, 21.56, 22.40, 29.33, 39.12, 48.27, 56.71, 59.29, 79.80, 84.76, 120.50, 139.30, 213.35; exact mass *m/z* calcd for $C_{11}H_{21}O_4$ (M - $C_7H_{11}OSSi$) 217.1440, found 217.1444.

(7*S,*E*)- and (7*S**,*Z*)-7-Ethenyl-3-(ethylidene)-7-[(triethylsilyl)oxy]bicylo[2.2.1]heptan-2-one [(*E*)-120 and (*Z*)-120].**

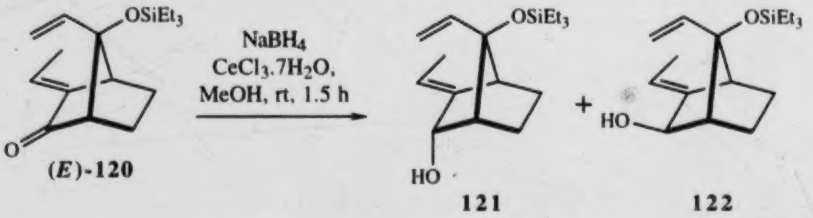


DBU (89.0 μL, 0.595 mmol) was added to a stirred solution of mesylate **119** (mixture of diastereomers, 115 mg, *ca* 0.296 mmol) in THF (3 mL). After 1 h, the mixture was diluted with Et_2O (5 mL) and washed successively with water, 10% aqueous hydrochloric acid, water, and brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 16 cm), using 1:20 EtOAc-hexane, gave α,β-unsaturated ketones (*E*)-**120** (64.2 mg, 74%) and (*Z*)-**120** (13.4 mg, 16%), as colorless oils. The major olefin [(*E*)-**120**] had: FTIR (CH_2Cl_2 cast) 2953, 1737, 1666, 1116 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.62 (q, *J* = 7.5 Hz, 6 H), 0.95 (t, *J* = 7.5 Hz, 9 H), 1.45 (ddd, *J* = 17.0, 10.0, 7.0 Hz, 2 H), 1.75 (d, *J* = 7.0 Hz, 3 H), 2.10-2.32 (m, 2 H), 2.59 (dd, *J* = 4.5, 1.5 Hz, 1 H), 2.98 (d, *J* = 4.0 Hz, 1 H), 5.16 (dd, *J* = 10.5, 1.2 Hz, 1 H), 5.20 (dd, *J* = 17.5, 1.2 Hz, 1 H), 6.00 (dd, *J* = 17.5, 10.5 Hz, 1 H), 6.28 (qd, *J* = 7.0, 0.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.68 (t'), 7.06 (q'), 14.52 (q'), 23.41 (t'), 27.04 (t'), 48.10 (d'), 57.91 (d'), 85.01 (s'), 118.44 (t'), 126.60 (d'), 138.51 (d'), 143.77 (s'), 202.84 (s'); exact mass *m/z* calcd for $C_{17}H_{28}O_2Si$ 292.1859, found 292.1855.

The minor olefin [(*Z*)-**120**] had: FTIR (CH_2Cl_2 cast) 2955, 1730, 1656, 1115 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.60 (q, *J* = 7.5 Hz, 6 H), 0.93 (t, *J* = 7.5 Hz, 9 H), 1.46 (d, *J* = 7.8 Hz, 2 H), 1.99 (d, *J* = 7.0 Hz, 3 H), 2.10-2.30 (m, 2 H), 2.59 (dd, *J* = 5.0, 1.9 Hz, 1 H), 2.69 (dd, *J* = 4.0, 1.5 Hz, 1 H), 5.18 (dd, *J* = 10.5, 1.0 Hz, 1 H), 5.23 (dd, *J* = 17.5, 1.0 Hz, 1 H), 5.80 (q, *J* = 7.0 Hz, 1 H), 6.01 (dd, *J* = 17.5, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.67 (t'), 7.05 (q'), 14.94 (q'), 22.84 (t'), 27.89 (t'), 53.52 (d'), 59.57 (d'), 84.52 (s'), 118.52 (t'), 132.12 (d'), 138.86 (d'), 142.03 (s'), 204.78 (s'); exact mass *m/z* calcd for $C_{17}H_{28}O_2Si$ 292.1859, found 292.1851.

NOTE: Olefins (*E*)-**120** and (*Z*)-**120** can be prepared conveniently from the parent ketone **117** without purification of the intermediate alcohol and mesylate in 60% [(*E*)-olefin) and 11% [(*Z*)-olefin) yield over the three steps.

(2*R,7*S**,*E*)- and (2*S**,7*S**,*Z*)-7-Ethenyl-3-(ethylidene)-7-[(triethylsilyl)oxy]bicylo[2.2.1]heptan-2-ol (121 and 122).**



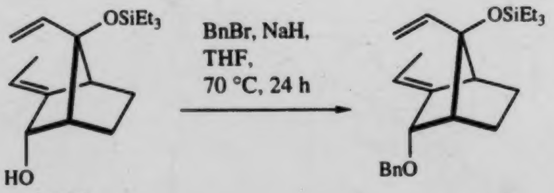
(*E*)-**120** **121** **122**

$NaBH_4$ (11.4 mg, 0.301 mmol) was added in small portions to a stirred solution of enone (*E*)-**120** (57.5 mg, 0.197 mmol) and $CeCl_3 \cdot 7H_2O$ (111 mg, 0.298 mmol) in MeOH (1.0 mL) at room temperature. After 1.5 h, the suspension was diluted with Et_2O (5 mL), and water (1 mL) was added. The aqueous phase was extracted with Et_2O (2 x 1 mL) and the combined organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 15 cm), using 1:10 EtOAc-hexane, gave alcohols **121** (24.3 mg, 42%) and **122** (25.7 mg, 44%) as colorless oils:

Endo alcohol **121** had: FTIR (CH_2Cl_2 cast) 3335, 2956, 1120, 1063, 725, 743 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.59 (q, *J* = 7.5 Hz, 6 H), 0.94 (t, *J* = 7.5 Hz, 9 H), 1.27 (ddd, *J* = 12.3, 8.3, 4.3 Hz, 2 H), 1.53 (br s, 1 H), 1.63 (dd, *J* = 7.0, 2.0 Hz, 2 H), 1.76-1.90 (m, 2 H), 2.04-2.16 (m, 2 H), 2.77 (d, *J* = 4.5 Hz, 1 H), 4.27 (br s, 1 H), 5.14 (dd, *J* = 10.5, 1.5 Hz, 1 H), 5.21 (dd, *J* = 17.5, 1.5 Hz, 1 H), 5.35 (qdd, *J* = 5.5, 1.5, 0.9 Hz, 1 H), 5.99 (dd, *J* = 17.5, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.82 (t'), 7.13 (q'), 14.32 (q'), 18.94 (t'), 28.27 (t'), 47.57 (d'), 51.29 (d'), 72.67 (d'), 85.29 (s'), 116.38 (d'), 117.22 (t'), 138.61 (d'), 148.87 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_2Si$ 294.2015, found 294.2011.

Exo alcohol **122** had: FTIR (CH_2Cl_2 cast) 3451, 2955, 1109, 776 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.59 (q, J = 7.5 Hz, 6 H), 0.93 (t, J = 7.5 Hz, 9 H), 1.13-1.26 (m, 2 H), 1.70-1.80 (m, 1 H), 1.74 (dd, J = 10.0, 1.4 Hz, 3 H), 2.04-2.13 (m, 3 H), 2.89 (br s, 1 H), 3.77 (d, J = 10.0 Hz, 1 H), 5.30 (dd, J = 10.5, 1.4 Hz, 1 H), 5.35 (dd, J = 17.0, 1.4 Hz, 1 H), 5.50 (qdd, J = 6.3, 1.4, 0.7 Hz, 1 H), 6.22 (dd, J = 17.0, 10.5 Hz, 1 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.80 (t'), 7.12 (q'), 14.48 (q'), 25.29 (t'), 26.48 (t'), 45.84 (d'), 53.80 (d'), 76.49 (d'), 86.61 (s'), 117.99 (t'), 118.62 (d'), 141.39 (d'), 150.15 (s'); exact mass *m/z* calcd for $C_{17}H_{30}O_2Si$ 294.2015, found 294.2010.

(2*S,7*S**,*E*)-7-Ethenyl-3-(ethylidene)-2-[(phenylmethyl)oxy]-7-[(triethylsilyl)oxy]bicylo[2.2.1]heptane (123).**

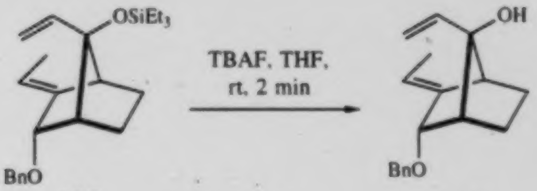


121

123

BnBr (60 µL, 0.50 mmol) was added to a stirred suspension of alcohol **121** (48.3 mg, 0.164 mmol) and NaH (97% w/w, 11.1 mg, 0.463 mmol) in THF (1.0 mL). The mixture was then heated at 70 °C for 24 h, cooled to room temperature, diluted with Et_2O, and quenched with water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 17 cm), using 1:40 EtOAc-hexane, gave benzyl ether **123** (59.2 mg, 94%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 1094, 727 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.60 (q, J = 8.0 Hz, 6 H), 0.95 (t, J = 8.0 Hz, 9 H), 1.33 (dd, J = 8.9, 4.1 Hz, 1 H), 1.64 (dd, J = 6.9, 2.0 Hz, 3 H), 1.77-1.90 (m, 2 H), 2.10 (ddd, J = 15.9, 11.0, 5.5 Hz, 1 H), 2.29 (app t, J = 3.7 Hz, 1 H), 2.76 (d, J = 4.3 Hz, 1 H), 4.07 (d, J = 2.0 Hz, 1 H), 4.34 and 4.46 (ABq, Δv = 34.8 Hz, J = 11.1 Hz, 2 H), 5.13 (dd, J = 10.6, 1.5 Hz, 1 H), 5.21 (dd, J = 17.6, 1.5 Hz, 1 H), 5.38 (qdd, J = 7.0, 2.1, 1.0 Hz, 1 H), 5.99 (dd, J = 17.6, 10.6 Hz, 1 H), 7.24-7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.83 (t'), 7.15 (q'), 14.33 (q'), 19.38 (t'), 28.13 (t'), 47.42 (d'), 48.11 (d'), 71.50 (t'), 79.78 (d'), 85.46 (s'), 117.17 (t'), 117.34 (d'), 127.80 (d'), 128.24 (d'), 128.61 (d'), 138.73 (d'), 139.36 (s'), 145.30 (s'); exact mass m/z calcd for $C_{24}H_{36}O_2Si$ 384.2485, found 384.2485.

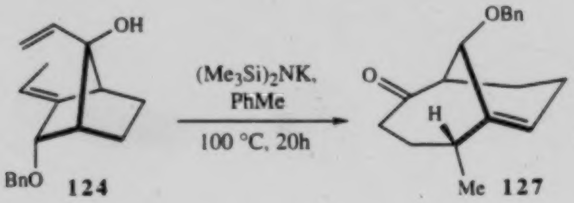
(2*S**,7*S**,*E*)-7-Ethenyl-3-(ethylidene)-2-[(phenylmethyl)oxy]-bicylo[2.2.1]heptan-7-ol (124).



123 124

TBAF (1.0 M in THF, 0.11 mL, 0.11 mmol) was added to a stirred solution of benzyl ether **123** (27.9 mg, 0.0725 mmol) in THF (1 mL). After 2 min, the mixture was diluted with Et_2O (2 mL) and washed with water and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 17 cm), using 1:10 EtOAc-hexane, gave alcohol **124** (17.5 mg, 89%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3431, 2954, 1091 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.40 (ddd, J = 13.0, 9.1, 3.5 Hz, 1 H), 1.64 (dd, J = 6.6, 1.8 Hz, 4 H), 1.82 (app dtd, J = 11.6, 4.2, 1.7 Hz, 1 H), 1.93 (ddd, J = 12.5, 9.1, 4.2 Hz, 1 H), 2.01 (dddd, J = 11.6, 11.6, 4.2, 4.2 Hz, 1 H), 2.28 (app td, J = 4.2, 0.8 Hz, 1 H), 2.67 (d, J = 4.2, 1 H), 4.21 (dd, J = 1.9, 1.9 Hz, 1 H), 4.35 and 4.47 (ABq, Δv = 33.7 Hz, J = 11.5, 2 H), 5.15 (dd, J = 10.9, 1.7 Hz, 1 H), 5.36 (dd, J = 17.3, 1.7 Hz, 1 H), 5.48 (qdd, J = 6.4, 1.5, 0.6 Hz, 1 H), 6.10 (dd, J = 17.3, 10.9 Hz, 1 H), 7.24-7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.41 (q'), 19.32 (t'), 27.96 (t'), 48.43 (d'), 48.65 (d'), 71.55 (t'), 79.99 (d'), 83.67 (s'), 115.76 (t'), 118.65 (d'), 127.86 (d'), 128.24 (d'), 128.63 (d'), 139.19 (s'), 139.62 (d'), 144.87 (s'); exact mass *m/z* calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1619.

(5*R,10*S**,*Z*)-5-Methyl-10-[(phenylmethyl)oxy]bicyclo-[4.3.1]dec-6-en-2-one (127).**

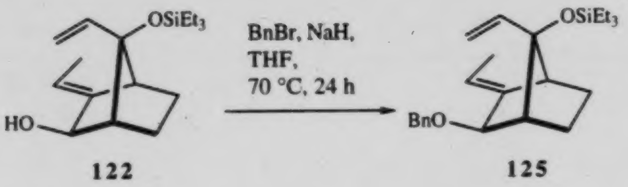


$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.16 mL, 0.080 mmol) was added to a stirred solution of alcohol **124** (17.5 mg, 0.0647 mmol) in PhMe (1 mL) at room temperature. The solution was then heated for 21 h (oil bath at 100 °C), cooled to room temperature, diluted with Et_2O (2 mL), and washed successively with saturated aqueous NH_4Cl, water, and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.1 x 17 cm), using 1:20 EtOAc-hexane, gave the bridgehead olefin **127** (16.6 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2930, 1704, 1453, 1087 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 1.00-1.16 (m, 1 H), 1.08 (d, J = 6.7 Hz, 3 H), 1.86-2.51 (m, 7 H), 2.74 (ddd, J = 15.3, 12.2, 3.1 Hz, 1 H), 2.87 (dd, J = 7.6, 4.4 Hz, 1 H), 4.40 and 4.48 (ABq, $\Delta\nu$ = 24.0 Hz, J = 11.3 Hz, 2 H), 4.58 (dd, J = 4.4, 1.4 Hz, 1 H), 5.67 (dq, J = 7.0, 1.7, 1.4 Hz, 1

H), 7.26-7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 16.78 (q'), 18.43 (t'), 20.69 (t'), 40.00 (d'), 42.40 (t'), 42.78 (t'), 51.90 (d'), 70.64 (t'), 78.90 (d'), 123.39 (d'), 127.87 (d'), 128.09 (d'), 128.67 (d'), 139.14 (s'), 147.67 (s'), 212.69 (s'); exact mass *m/z* calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1625.

Note: The use of 18-crown-6 did not seem to accelerate the reaction and, in the one experiment tried, gave a lower yield (78%).

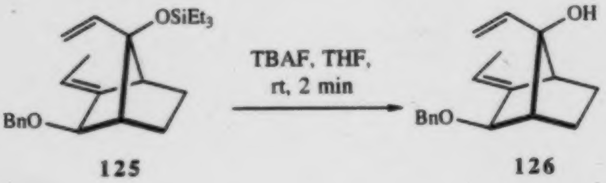
(2*R,7*S**,*E*)-7-Ethenyl-3-(ethylidene)-2-[(phenylmethyl)oxy]-7-[(triethylsilyl)oxy]bicylo[2.2.1]-heptane (125).**



BnBr (60 μL, 0.52 mmol) was added to a stirred suspension of alcohol **122** (48.5 mg, 0.165 mmol) and NaH (97% w/w, 11.1 mg, 0.463 mmol) in THF (1 mL). The mixture was then heated at 70 °C for 24 h, cooled to room temperature, diluted with Et_2O, and quenched with water. The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.7 x 16 cm), using 1:40 EtOAc-hexane, gave benzyl ether **125** (50.0 mg, 79%) as a colorless oil: FTIR (CH_2Cl_2 cast) 2954, 1098, 731

cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 0.61 (q, *J* = 7.9 Hz, 6 H), 0.96 (t, *J* = 7.9 Hz, 9 H), 1.12 (app dq, *J* = 27.0, 5.3 Hz, 2 H), 1.66 (dd, *J* = 6.5, 1.5 Hz, 3 H), 2.00-2.07 (m, 2 H), 2.24 (d, *J* = 3.1 Hz, 1 H), 2.86 (d, *J* = 1.8 Hz, 1 H), 3.72 (s, 1 H), 4.40 and 4.54 (ABq, Δv = 41.2 Hz, *J* = 12.0 Hz, 2 H), 5.10 (dd, *J* = 10.9, 1.8 Hz, 1 H), 5.20 (dd, *J* = 17.5, 1.8 Hz, 1 H), 5.42 (qdd, *J* = 6.9, 1.4, 0.7 Hz, 1 H), 6.23 (dd, *J* = 17.5, 10.9 Hz, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 6.89 (t'),7.20 (q'), 14.45 (q'), 25.24 (t'), 27.05 (t'), 46.66 (d'), 49.12 (d'), 71.52 (t'), 83.48 (d'), 87.12 (s'), 115.62 (d'), 119.04 (d'), 127.67 (d'), 128.17 (d'), 128.58 (d'), 139.60 (s'), 140.57 (d'), 146.29 (s'); exact mass *m/z* calcd for $C_{24}H_{36}O_2Si$ 384.2485, found 384.2482.

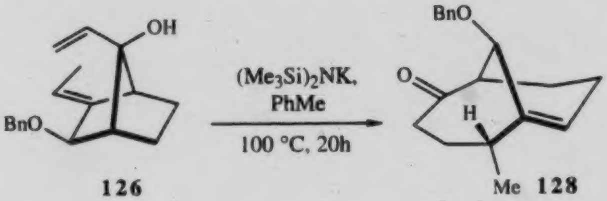
(2*R,7*S**,*E*)-7-Ethenyl-3-(ethylidene)-2-[(phenylmethyl)oxy]-bicylo[2.2.1]heptan-7-ol (126).**



TBAF (1.0 M in THF, 0.06 mL, 0.06 mmol) was added to a stirred solution of benzyl ether **125** (23.4 mg, 0.0608 mmol) in THF (1 mL). After 2 min, the mixture was diluted with Et_2O (2 mL) and washed with water and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 17 cm), using 1:10

EtOAc-hexane, gave alcohol **126** (15.6 mg, 95%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3425, 2972, 1092 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.80-1.30 (m, 2 H), 1.60 (br s, 1 H), 1.66 (dd, *J* = 7.0, 1.6 Hz, 3 H), 2.04-2.12 (m, 2 H), 2.20 (d, *J* = 4.8 Hz, 1 H), 2.66 (d, *J* = 2.7 Hz, 1 H), 3.79 (br s, 1 H), 4.42 and 4.58 (ABq, $\Delta\nu$ = 46.6 Hz, *J* = 11.4 Hz, 2 H), 5.08 (dd, *J* = 10.9, 1.7 Hz, 1 H), 5.32 (dd, *J* = 17.4, 1.7 Hz, 1 H), 5.55 (qdd, *J* = 6.5, 1.6, 1.0 Hz, 1 H), 6.56 (dd, *J* = 17.4, 10.9 Hz, 1 H), 7.24-7.38 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 14.53 (q'), 25.18 (t'), 27.07 (t'), 48.57 (d'), 49.18 (d'), 71.67 (t'), 84.05 (d'), 85.14 (s'), 112.35 (t'), 120.24 (d'), 127.74 (d'), 128.16 (d'), 128.60 (d'), 139.43 (s'), 142.43 (d'), 145.94 (s'); exact mass *m/z* calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1618.

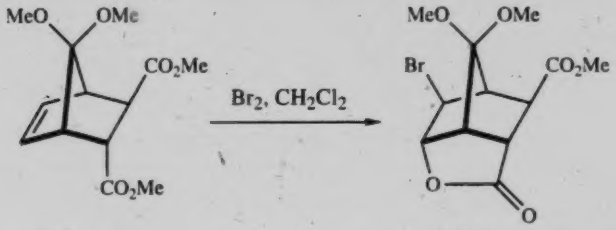
(5*R**,10*R**,*Z*)-5-Methyl-10-[(phenylmethyl)oxy]bicyclo[4.3.1]dec-6-en-2-one (128).



$(Me_3Si)_2NK$ (0.5 M in PhMe, 0.16 mL, 0.080 mmol) was added to a solution of alcohol **126** (18.0 mg, 0,0667 mmol) in PhMe (1 mL) at room temperature. The solution was then heated for 20 h (oil bath at 100 °C), cooled to room temperature, diluted with Et_2O (2 mL), and washed successively with saturated aqueous NH_4Cl, water, and brine. The organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.0 x 17 cm), using 1:20 EtOAc-hexane, gave the bridgehead olefin **128** (14.7 mg, 82%) as white crystals: FTIR (CH_2Cl_2 cast) 3031, 2847, 1695, 1113, 1097 cm^{-1}; ^1H NMR (300 MHz, CD_2Cl_2) δ 0.8-1.14 (m, 1 H), 1.08 (d, *J* = 6.6 Hz, 3 H), 1.80-2.23 (m, 6 H), 2.79 (dd, *J* = 7.0, 2.5 Hz, 1 H), 3.01 (ddq, *J* = 15.0, 7.0, 7.0 Hz, 1 H), 3.25 (ddd, *J* = 14.5, 11.0, 3.0 Hz, 1 H), 3.99 (t, *J* = 2.0 Hz, 1 H), 4.64 and 4.66 (ABq, Δv = 5.0 Hz, *J* = 12.5 Hz, 2 H), 5.56 (d, *J* = 7.5 Hz, 1 H), 7.25-7.45 (m, 5 H); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 17.24 (q'), 20.79 (t'), 24.13 (t'), 32.39 (d'), 41.58 (t'), 42.74 (t'), 51.81 (d'), 72.26 (t'), 78.66 (d'), 119.08 (d'), 127.72 (d'), 127.94 (d'), 128.76 (d'), 138.82 (s'), 150.87 (s'), 215.31 (s'); exact mass *m/z* calcd for $C_{18}H_{22}O_2$ 270.1620, found 270.1617.

Note: The use of 18-crown-6 did not seem to accelerate the reaction and, in the one experiment tried, gave a lower yield (65%).

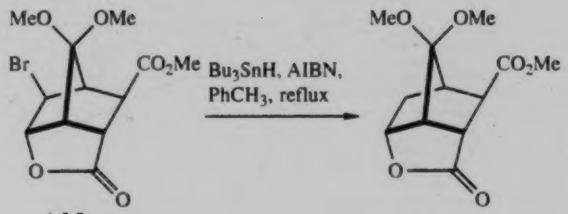
(3-*exo*, 5-*exo*)-5-Bromo-6-hydroxy-7,7-dimethoxy-3-methoxycarbonyl-2-norbornanecarboxylic acid γ-lactone (139).



129 139

A solution of Br_2 (1.85 g, 11.6 mmol) in CH_2Cl_2 (2 mL) was added dropwise over 20 min to a stirred and cooled (0 °C) solution of diester **129** (2.93 g, 8.75 mmol) in CH_2Cl_2 (20 mL). After 3 h, no starting material could be detected (TLC control, silica, 2:3 EtOAc-hexane). The mixture was quenched with 10% aqueous Na_2SO_3 and the aqueous phase was extracted with CH_2Cl_2 (2 x 5 mL). The organic phase was washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 2:3 EtOAc-hexane, gave bromolactone **139** (2.35 g, 80%) as a white solid: mp 154-160 °C; FTIR (CH_2Cl_2 cast) 1803, 1787, 1739 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 2.69 (d, J = 2.5, 1 H), 3.17-3.21 (m, 4 H), 3.22-3.26 (m, 1 H), 3.29 (s, 3 H), 3.32-3.36 (m, 1 H), 3.75 (s, 3 H), 3.85 (s, 1 H), 5.40 (dm, J = 5.0 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 39.46, 48.92, 49.22, 49.84, 50.47, 51.07, 51.97, 52.90, 87.20, 113.21, 169.92, 176.92; exact mass m/z calcd for $C_{12}H_{15}O_6$ (M - Br) 255.0869, found 255.0870.

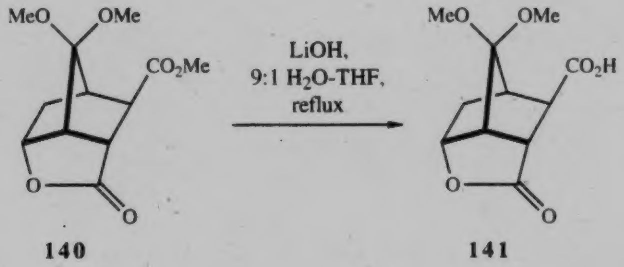
(3-*exo*)-6-Hydroxy-7,7-dimethoxy-3-methoxycarbonyl-2-norbornanecarboxylic acid γ-lactone (141).



139 **140**

A solution of bromolactone **139** (2.13 g, 6.35 mmol), Bu_3SnH (2.06 mL, 7.66 mmol), and AIBN (50.0 mg, 0.305 mmol) in PhH (20 mL) was stirred and refluxed for 12 h. The mixture was then cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (5 x 15 cm), using 1:2.5 EtOAc-hexane, gave lactone **140** (1.19 g, 73%) as a white, crystalline solid: mp 101-103 °C; FTIR (CH_2Cl_2 cast) 1780 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.52 (d, J = 14.0 Hz, 1 H), 2.26 (ddd, J = 14.5, 7.1, 4.0 Hz, 1 H), 2.64 (d, J = 2.0 Hz, 1 H), 2.88 (app d quintet, J = 4.5, 0.5 Hz, 1 H), 3.12 (td, J = 5.0, 1.5 Hz, 1 H), 3.17 (s, 3 H), 3.23 (s, 3 H), 3.29-3.33 (m, 1 H), 3.70 (s, 3 H), 4.79-4.4.83 (m, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 35.48, 40.81, 42.92, 48.44, 49.41, 51.17, 52.56, 79.42, 113.94, 171.53, 178.64 (two signals overlap); exact mass m/z calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0949.

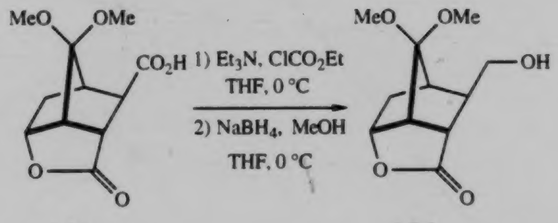
(3-*exo*)-6-Hydroxy-7,7-dimethoxy-3-carboxy-2-norbornanecarboxylic acid γ-lactone (141).



Water (5 mL) was added to a stirred solution of ester **140** (490.0 mg, 1.912 mmol) and LiOH·H_2O (170.3 mg, 4.058 mmol) in THF (5 mL). The mixture was then stirred and refluxed (85 °C) for 30 min, cooled to room temperature and diluted with Et_2O (10 mL). The mixture was acidified by dropwise addition of concentrated hydrochloric acid to pH 1 (litmus paper). The aqueous phase was extracted with Et_2O (3 x 5 mL) and the combined organic phases were washed with water (5 mL) and brine (5 mL), dried ($MgSO_4$) and evaporated. The resulting crude carboxylic acid **141** (462.1 mg, *ca*. 100%) was used without further purification in the next step. Flash chromatography of a small sample over silica gel, using 1:19 MeOH-CH_2Cl_2, gave carboxylic acid **141** as a foam: FTIR (CH_2Cl_2 cast) 3200, 1780, 1739, 1707 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.55 (d, *J* = 14.5 Hz, 1 H), 2.27 (ddd, *J* = 14.0, 7.5, 4.0 Hz, 1 H), 2.75 (d, *J* = 2.0 Hz, 1 H), 2.92 (d, *J* = 4.5 Hz, 1 H), 3.16 (td, *J* = 1.3 Hz, 5.1 Hz, 1 H), 3.21 (s, 3 H), 3.25 (s, 3 H), 3.28-3.32 (m, 1 H), 4.84 (app t, *J* = 6.0 Hz, 1 H), 7.00-

12.00 (br s, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 35.31, 40.65, 42.99, 48.99, 49.21, 51.24, 79.48, 113.91, 176.79, 178.44 (two signals overlap); exact mass *m/z* calcd for $C_{11}H_{14}O_6$ 242.0790, found 242.0790.

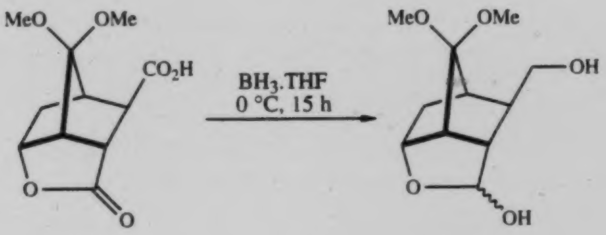
(3-*exo*)-6-Hydroxy-3-hydroxymethyl-7,7-dimethoxy-2-norbornanecarboxylic acid γ-lactone (134).



141 **134**

Neat $EtCO_2Cl$ (12 μL, 0.13 mmol) was added in one portion to a stirred and cooled (0 °C) solution of carboxylic acid **141** (30.0 mg, 0.124 mmol) and Et_3N (0.02 mL, 0.1 mmol). The reaction was monitored by TLC (silica, 1:19 MeOH-CH_2Cl_2) and, after 30 min, no more starting material could be detected. The white suspension was filtered directly into a 5 mL syringe equipped with a filtration tip [0.2 μm, Milex-FGS microfilter (Millipore)], the flask was rinsed with THF (3 x 1 mL), and the rinsing was taken up into the same partially filled syringe. The clear filtrate was then added to $NaBH_4$ (20.3 mg, 0.537 mmol). The mixture was then cooled (0 °C) and MeOH (0.07 mL, 2 mmol) was added with stirring. The reaction was monitored by TLC (silica, 2:3 EtOAc-hexane) and, after 1.25 h, no starting material could be detected. The mixture was acidified by dropwise addition of 10% aqueous hydrochloric acid to pH 2 (litmus paper). The aqueous phase was extracted with Et_2O (2 x 5 mL), and the combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. The ^1H NMR spectrum of the crude residue showed a nearly 1:1 mixture of the desired alcohol **134** and starting carboxylic acid **141**. The products were not separated and the identity of the alcohol was established by comparison with an authentic sample obtained later (see below).

(2aα,3α,4β,6α)-Hexahydro-2-hydroxy-5,5-dimethoxy-4,6-methanocyclopenta[c]furan-3-ylmethanol (143).

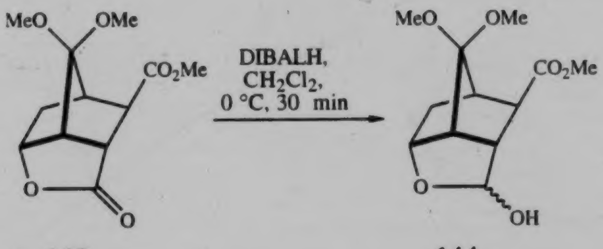


141 **143**

$BH_3 \cdot THF$ (1.0 M in THF, 6.0 mL, 6.0 mmol) was added dropwise to a stirred and cooled (0 °C) solution of carboxylic acid **141** (468.2 mg, 1.933 mmol) in THF (5 mL). Stirring was continued for 15 min at 0 °C, and the cold bath was removed. After 15 h, the mixture was cooled (0 °C), quenched with 1:1 THF-H_2O (2 mL), and diluted with Et_2O (10 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 15 cm), using 1:9 MeOH-

CH_2Cl_2, gave lactol-alcohol **143** (291.3 mg, 65%) as a colorless oil: FTIR 3436, 2944 cm^{-1}; ^{1}H NMR (300 MHz, CD_2Cl_2) δ 1.19 (d, *J* = 12.5 Hz, 2 H), 1.61-1.65 (m, 1 H), 1.96-2.00 (m, 1 H), 2.08-2.12 (m, 1 H), 2.19 (t, *J* = 4.0 Hz, 1 H), 2.92-2.94 (m, 1 H), 3.17 (s, 3 H), 3.27 (s, 3 H), 3.69 (d, *J* = 7.3 Hz, 2 H), 4.50 (t, *J* = 6.0 Hz, 1 H), 5.20 (s, 1 H) (one of the hydroxyls could not be detected under the experimental conditions); ^{13}C NMR (75.5 MHz, CD_2Cl_2) δ 38.94, 39.81, 46.96, 47.96, 48.77, 50.49, 50.58, 65.58, 103.17, 114.91 (two signals overlap); exact mass *m/z* calcd for $C_{11}H_{18}O_5$ 230.1154, found 230.1157.

Methyl (2aα,3α,4β,6α)-Hexahydro-2-hydroxy-5,5-dimethoxy-4,6-methanocyclopenta[c]furan-3-ylcarboxylate (144).

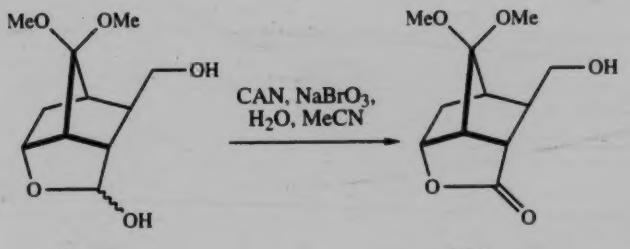


140 144

DIBAL-H (1.0 M in THF, 2.70 mL, 2.70 mmol) was added dropwise to a stirred and cooled (0 °C) solution of methyl ester **140** (344.5 mg, 1.344 mmol) in CH_2Cl_2 (10 mL). Stirring was continued for 30 min and the mixture was then quenched with cold (*ca.* 4 °C) 10% aqueous hydrochloric acid. The gelatinous suspension was filtered through a small pad of

Celite, and the residue was washed with CH_2Cl_2 (5 x 1 mL). The combined organic phases were washed with brine (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 15 cm), using 1:19 MeOH-CH_2Cl_2, gave lactol **144** (264.1 mg, 75%) as a colorless oil: FTIR (CH_2Cl_2 cast) 3425, 2953, 1735, 1065 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 300 MHz) δ 1.19 (d, J = 13.5 Hz, 2 H), 2.00 (ddd, J = 13.0, 7.0, 4.0 Hz, 1 H), 2.22 (d, J = 2.6 Hz, 1 H), 2.68 (d, J = 4.0 Hz, 1 H), 2.93-2.97 (m, 1 H), 3.17 (s, 3 H), 3.19 (s, 3 H) 3.65 (s, 3 H), 4.50 (app t, J = 6.0 Hz, 1 H), 5.22 (d, J = 4.0 Hz, 1 H) (the signal corresponding to the hydroxyl could not be discerned); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 37.33, 41.18, 46.99, 47.27, 49.22, 50.74, 50.86, 52.12, 79.28, 102.78, 114.42, 173.39; exact mass m/z calcd for $C_{12}H_{18}O_6$ 258.1103, found 258.1107.

(3-*exo*)-6-Hydroxy-3-hydroxymethyl-7,7-dimethoxy-2-norbornanecarboxylic acid γ-lactone (134).



143 **134**

$NaBrO_3$ (326 mg, 2.17 mmol) and CAN (119 mg, 0.217 mmol) were added to a stirred solution of lactol-alcohol **143** (500 mg, 2.17 mmol) in 7:3 v/v MeCN-H_2O (12 mL). The mixture was refluxed (oil bath, 90 °C) with stirring for 7 h, at which point no starting material remained (TLC control, 1:9 MeOH-CH_2Cl_2). The mixture was then cooled to room temperature, diluted with Et_2O (50 mL), and extracted with saturated aqueous $NaHCO_3$. The aqueous phase was extracted with Et_2O (2 x 10 mL) and the combined organic phases were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2.0 x 15 cm), using 1:19 MeOH-CH_2Cl_2, gave alcohol **134** (178.7 mg, 36%) as a yellow oil: FTIR (CH_2Cl_2 cast) 3428, 1785 cm^{-1}; ^1H NMR (CD_2Cl_2, 300 MHz) δ 1.46 (d, J = 12.5 Hz, 1 H), 2.09 (td, J = 2.5, 7.2 Hz, 1 H), 2.22-2.26 (m, 1 H), 2.36 (d, J = 4 Hz, 1 H), 2.45-2.48 (m, 1 H), 3.13 (td, J = 5.5, 1.5 Hz, 1 H), 3.21 (s, 3 H), 3.26 (s, 3 H), 3.76 (d, J = 7.0 Hz, 2 H), 4.78-4.82 (m, 1 H) (the signal corresponding to the hydroxyl could not be discerned); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) δ 37.34, 41.39, 42.09, 50.13, 50.83, 50.97, 65.11, 79.79, 114.49, 176.08 (two signals overlap); exact mass m/z calcd for $C_{11}H_{16}O_5$ 228.0998, found 228.1029.

IV. References and footnotes.

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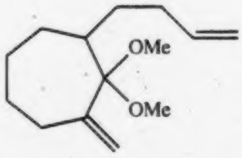

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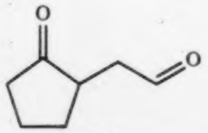

112

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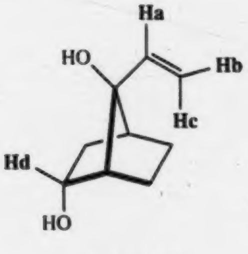

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102. Phosphomolybdic acid (15 g) and ceric ammonium sulfate (2.5 g) dissolved in a mixture of water (485 mL) and concentrated sulfuric acid (15 mL).

103. 2,4-Dinitrophenylhydrazine (0.4 g) dissolved in 100 mL 2N HCl.